

# **EXHIBIT A40**



# An evaluation of the risks of lung cancer and mesothelioma from exposure to amphibole cleavage fragments

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Received 5 September 2007

Available online 22 October 2007

## Abstract

Amphiboles are hydrated mineral silicates five of which occur in asbestiform habits as asbestos grunerite (amosite) asbestos, riebeckite (crocidolite) asbestos, anthophyllite asbestos, tremolite asbestos and actinolite asbestos] and non-asbestiform habits (grunerite, riebeckite, anthophyllite, tremolite and actinolite). The asbestiform varieties are characterized by long, thin fibers while non-asbestiform varieties such as cleavage fragments form short fibers with larger widths. The U.S. regulatory method for counting asbestos fibers (aspect ratio  $\geq 3:1$ , length  $\geq 5 \mu\text{m}$ ) does not distinguish between asbestos and cleavage fragments. The method biases toward increased counts of non-asbestiform cleavage fragments compared to long, thin asbestos fibers. One consequence of this regulatory approach is that workers can be erroneously classified as exposed to concentrations of asbestos (asbestiform amphiboles) above the U.S. 0.1 f/mL exposure standard when in fact they are not exposed to asbestos at all but non-asbestiform amphibole cleavage fragments. Another consequence is that the known carcinogenic effects of asbestos may be falsely attributed to non-asbestiform amphibole cleavage fragments of the same mineral. The purpose of this review is to assess whether amphibole cleavage fragments pose the same risk of lung cancer and mesothelioma characteristic of amphibole asbestos fibers.

We identified three groups of workers exposed to non-asbestiform amphiboles: two groups exposed to grunerite (Homestake gold miners and taconite miners) and one group exposed to industrial talc containing non-asbestiform tremolite and anthophyllite in St. Lawrence County, NY. In addition to assessing strength of association and exposure–response trends in the non-asbestiform amphibole cohorts, comparisons were also made with cohorts exposed to the asbestiform counterpart (positive control) and cohorts exposed to the mineral (e.g. talc) that does not contain amphiboles (negative controls).

The cohorts exposed to non-asbestiform amphiboles had no excesses of lung cancer or mesothelioma. Similar results were observed in the negative control groups, in stark contrast to the excess risks of asbestos-related disease found in the asbestos cohorts. The only possible exception is the twofold increased risk of lung cancer where exposure was to industrial talc containing cleavage fragments of tremolite and anthophyllite. However, this risk is not considered attributable to the talc or amphibole cleavage fragments for several reasons. A similar increased risk of lung cancer was found in Vermont talc workers, studied in the same time period. Their exposure was to relatively pure talc. There was no relationship between lung cancer mortality and exposure measured as  $\text{mg}/\text{m}^3$  years and years worked. A case–control study reported that all the lung cancer cases were smokers (or former smokers) and attributed the excess to smoking. There were two mesothelioma cases among the NY State talc workers exposed to cleavage fragments of tremolite and anthophyllite, but talc is not a plausible cause because of too short latency and potential for previous asbestos exposure. The positive controls of tremolite asbestos and anthophyllite asbestos exposed workers showed excess risks of both lung cancer and mesothelioma and positive exposure–response trends. St. Lawrence, NY talc does not produce mesotheliomas in animals while amphibole asbestos does. In sum, the weight of evidence fully supports a conclusion that non-asbestiform amphiboles do not increase the risk of lung cancer or mesothelioma.

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**Keywords:** Amphiboles; Cleavage fragments; Lung cancer; Mesothelioma; Asbestos; Non-asbestiform amphiboles; Grunerite; Talc

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## 1. Introduction

Asbestos is a generic term applied to a group of hydrated fibrous mineral silicates. Their asbestiform habit permits them to be easily separated into long, thin, flexible, strong fibers and ultimately fibrils (single fibers). Included are the asbestiform serpentine (chrysotile) and the asbestiform amphiboles, riebeckite (crocidolite) asbestos, anthophyllite asbestos, grunerite (amosite) asbestos, tremolite asbestos and actinolite asbestos. These minerals also crystallize with non-asbestiform habits, their counterparts being lizardite or antigorite (chrysotile), riebeckite, anthophyllite, grunerite, tremolite and actinolite, respectively. Crystal habit is a description of the shapes in which a certain mineral is likely to occur, both in nature and when grown synthetically. Tremolite is a mineral in the tremolite–ferro-actinolite series that has fewer than 0.5 atoms of iron, and more than 4.5 atoms of magnesium per formula unit; actinolite has between 0.5 and 2.5 atoms of iron, and 2.5 atoms of magnesium per formula unit; ferro-actinolite has more than 2.5 atoms of iron per formula unit with the balance being magnesium.

By the early 1970s, airborne concentrations of asbestos fiber were being measured using “the membrane filter phase contrast method (PCM)”. In many countries, including the USA, this method was adopted for the regulatory control of asbestos. Fundamental to the method was the definition of a fiber as an elongated particle having a length: breadth ratio (aspect ratio) of at least 3:1 and a minimum length of 5 micrometers ( $\mu\text{m}$ ). Such a definition does not allow the microcopist to distinguish between asbestos fibers and non-asbestos amphibole particles. Consequently, in work environments where there exist many elongated particles meeting the PCM fiber definition, they are counted as if they are “asbestos” even if they are neither asbestos minerals nor even amphiboles. This results in concern by workers and health professionals about health risks and potential economic impacts for companies mining ore deposits where amphibole minerals are present. This is because the amphiboles have cleavage planes such that when they are crushed they produce elongated prismatic particles called cleavage fragments.

All amphiboles that were once exploited commercially as asbestos have non-asbestiform counterparts. Hence, workers in industries where amphibole cleavage fragments are present, but not asbestos, are often erroneously reported as being exposed to asbestos based on current regulatory counting strategies and protocols. On the other hand, the evidence concerning the health consequences of exposure to cleavage fragments has never been widely understood. Industries involving exposure to cleavage fragments should not be exempt from similar controls to the asbestos industries, if elongated particles meeting the PCM definition of fibers pose qualitatively and quantitatively the same levels of health risk as their asbestiform counterparts. However, if cleavage fragments pose no or

a lesser risk than the asbestos minerals, they should be regulated accordingly.

The purpose of this paper is to compare, as far as possible, the cancer risks (lung cancer and mesothelioma) for workers exposed to airborne amphibole cleavage fragments with those associated with exposure to amphibole analogues that formed asbestos fibers. Pneumoconiosis risk will not be compared because some of the minerals associated with the amphibole cleavage fragments are recognized in their own right as causing lung fibrosis (e.g.: talc and crystalline silica). However, pneumoconiosis is sometimes used to assess whether exposure is high enough and latency long enough to detect carcinogenic risk and to evaluate the exposure–response.

## 2. Methods

The extent to which the carcinogenic risks of exposure to cleavage fragments differ from those associated with exposure to asbestos was examined in several ways.

The potential of particles to cause health effects depends on the characteristics of the particles (e.g.: size, shape, respirability, solubility, toxicity, carcinogenic potential), the level and duration of exposure as well as host and other factors. It is important to determine whether amphibole cleavage fragments differ sufficiently from asbestos fibers for them to pose different levels of health risk than their asbestos counterparts. To do this requires examination of the characteristics of the particle such as dimensions, shape and density that influence fiber respirability, and fiber dimensions and biopersistence that influence carcinogenicity.

Mesothelioma and lung cancer are the health endpoints examined for comparison of the relative effects of non-asbestiform and asbestiform amphiboles. Mesothelioma is considered the more important indicator because it is both more specific and perhaps more sensitive than lung cancer. Mesothelioma is a rare cancer that acts as a marker or “signal” tumor, which is primarily associated with exposure to amphibole asbestos and has occurred in some situations after what appears to be exposure at quite low concentrations. Lung cancer is more subject to being caused by confounding exposures such as smoking, which is the primary cause of lung cancer. Thus while lung cancer might be caused by asbestos, it is an effect that is not specific to asbestos exposure.

If smoking prevalence is not known, the effects of dust exposure and smoking in the occurrence of lung cancer cannot readily be distinguished. Mesothelioma is a more sensitive and specific indicator of amphibole asbestos exposure than lung cancer in that pleural mesothelioma may occur following what are ostensibly brief exposures (Roggli, 1990) and up to 80% of the cases in males may be associated with asbestos exposure (Price and Ware, 2004). The exposure–response curve is thought to be non-linear for both mesothelioma and lung cancer. While the shapes of relationships are still subject to debate, pleural mesothelioma has been reported to increase less than linearly with cumulative dose. For peritoneal mesothelioma the risk is thought to be proportional to the square of cumulative exposure while for lung cancer the exposure–response lies between linear and square of cumulative exposure (Hodgson and Darn-ton, 2000). As some mesothelioma have been reported to occur after relatively low and perhaps brief exposures one might anticipate that if amphibole cleavage fragments act like asbestos in causing mesothelioma there might be some cases even if cleavage fragment exposures were low. For mesothelioma to be attributed to amphibole cleavage fragments the time since first exposure must be more than about 20 years and there should be no previous exposure to asbestos or other confounding etiological factors.

The mortality from lung cancer and mesothelioma are compared to that expected in age- and sex-adjusted external populations. The comparison measure is the standardised observed/expected mortality ratio or standardized mortality ratio (SMR). When the incidence of lung cancer

and mesothelioma are compared to that expected in age- and sex-adjusted external populations, the comparison measure is the standardised observed/expected cancer incidence ratio or standardized incidence ratio (SIR). External comparisons for assessing lung cancer risk have inherent limitations such as differences in smoking and lifestyle between the study population and the external referent population. It is generally not feasible to adjust for these differences. An SMR less than 1.5 or a statistically non-significant SMR is suggestive, but not conclusive, of no association. A deficit in the lung cancer SMR could be due to exposure levels below a no-effect threshold, or a few highly exposed workers diluted by many workers with low exposure or negative confounding due to a low prevalence of smoking. A nonsignificant SMR might be due to the small size of the study population and the low power of the study to detect significant differences. Similarly, a positive finding of lung cancer could be due to differences in smoking prevalence between the study and reference populations rather than exposure to non-asbestiform amphiboles.

For mesothelioma, external comparisons using an SMR are often not possible because the expected number of cases is not known or not estimated. Therefore an internal proportional mortality ratio (PMR) is used to estimate risk of mesothelioma. PMR's have their limitations which must be taken into account when using them. For example, as a PMR can increase with length of follow-up of a cohort, attention must be given to the comparability of the follow-up period. Age differences in populations being compared are important as age determines the nature of diseases from which people die as well as the frequency of death. The ratio with total deaths to some extent adjusts for both differences in follow-up and age. Era of death may be important because of diagnostic trends. Nevertheless, comparison of PMRs between non-asbestiform amphibole-exposed and asbestos-exposed populations is a useful way to examine the question of whether non-asbestiform amphiboles cause cancer at the same rates as asbestiform amphiboles.

The actual measured risks of lung cancer and mesothelioma in persons exposed to amphibole cleavage fragments is compared to workers exposed to asbestiform amphiboles as follows:

- The lung cancer and mesothelioma experience of workers exposed to amphibole cleavage fragments is compared with the experience of workers exposed to their asbestiform equivalents. There are three main ore bodies containing non-asbestiform amphiboles where epidemiological studies have been conducted. These are a gold mine in South Dakota (grunerite-cummingtonite exposure), taconite mines in Minnesota (grunerite and other non-asbestiform amphiboles) and a talc mine in St Lawrence County, New York State (transition minerals, non-asbestiform anthophyllite and tremolite). Their experience was compared to that of workers exposed to asbestiform amphiboles. These “positive controls” were in amosite asbestos mines, mills and manufacturing facilities, anthophyllite asbestos mines and vermiculite mines (exposed to winchite asbestos also known as soda tremolite asbestos). In this report, winchite asbestos from the vermiculite mine in Montana, will be referred to as “tremolite asbestos” as this has been the terminology used in the medical literature.
- The mortality from lung cancer is examined in relation to estimated levels of exposure to “fibers” for workers exposed to asbestos and workers exposed to amphibole cleavage fragments. The existence of a positive gradient of increasing risk with increasing exposure after taking account of potential confounders would be good evidence that the cleavage fragments were posing an increased risk of lung cancer. A negative gradient would be strong evidence against a causal association. The presence or absence of an exposure-response gradient is among the strongest evidence for or against a lung cancer association with cleavage fragment exposure because smoking is the major cause of lung cancer and rarely, if ever, can external comparisons be fully adjusted for smoking.
- The lung cancer and mesothelioma experience of workers exposed to dusts from an ore-body containing amphibole cleavage fragments is compared with that of workers exposed to dusts from a similar ore-body which does not contain asbestos or amphibole cleavage fragments. This is called a negative control. If the experience of the amphibole

cleavage fragment exposed workers were worse than that of the negative control (non-cleavage fragment exposed workers), this would be suggestive of an increased risk due to the presence of asbestos cleavage fragments.

- In order to investigate this, the mortality for St. Lawrence County talc miners is compared to that of talc miners where it is claimed amphiboles are not present. Also, the mortality of iron ore miners exposed to taconite rocks containing non-asbestiform grunerite and actinolite is compared to that of miners exposed to iron ore (hematite) which does not contain amphiboles.
- The biological plausibility of a difference in the potential of amphibole cleavage fragments to cause cancer compared to amphibole asbestos fibers was assessed by review of the results of toxicological studies involving asbestos and amphibole cleavage fragments. There is a clear pattern of an increased incidence of mesothelioma in animals exposed to amphibole asbestos. Observing a similar pattern for animals exposed to non-asbestiform amphiboles would be evidence supporting the hypothesis that non-asbestiform amphiboles pose a carcinogenic hazard similar to asbestos. The lack of an increased incidence of mesothelioma would be strong evidence against the hypothesis.

### 3. The amphiboles

The crystallographic structure of amphiboles consists of double chains of silica tetrahedra. Their general chemistry incorporates  $(\text{Si}, \text{Al})_8\text{O}_{22}(\text{OH})_2$ . The amphibole group of minerals is made up of a number of mineral series. These series result from the substitution of different elements in the structure. For example tremolite and actinolite are part of a homologous series of minerals—tremolite–actinolite–ferro-actinolite with chemistry  $\text{Ca}_2(\text{MgFe})_5\text{Si}_8\text{O}_{22}(\text{OH})_2$ . Actinolite is  $\text{Ca}_2(\text{Mg}_{4.5}\text{Fe}_{0.5})\text{Si}_8\text{O}_{22}(\text{OH})_2$ – $\text{Ca}_2(\text{Mg}_{2.5}\text{Fe}_{2.5})\text{Si}_8\text{O}_{22}(\text{OH})_2$ . Ferro-actinolite is  $\text{Ca}_2(\text{Mg}_{2.5}\text{Fe}_{2.5})\text{Si}_8\text{O}_{22}(\text{OH})_2$ – $\text{Ca}_2\text{Fe}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$ . Actinolite with less than  $\text{Fe}_{0.5}$  would be tremolite.

In practice, these minerals can have a fairly wide range of composition within the broad range of substitutions possible. The mineral names are defined where the ranges of the substituted elements fall within certain arbitrary boundaries.

Grunerite is a member of the mineral series cummingtonite–grunerite with chemistry  $(\text{MgFe})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$ . As noted above, the asbestiform variety of grunerite is “amosite”. As with the tremolite–ferro-actinolite series, the minerals in this series may display a range of compositions.

Anthophyllite occurs as asbestos and in a non-fibrous form and is an end member of the anthophyllite–ferro-anthophyllite series, which is chemically  $(\text{MgFe}^{2+})_7\text{Si}_8\text{O}_{22}(\text{OH})_2$ . Anthophyllite is the name reserved for the orthorhombic  $\text{MgFe}$  amphibole where the ratio of  $\text{Mg}/(\text{Mg} + \text{Fe})$  is greater than 0.5; a lower amount of magnesium in the same type of amphibole requires the name ferro-anthophyllite.

Non-asbestiform riebeckite and crocidolite asbestos have the same chemistry which is  $\text{Na}_2\text{Fe}_3^{2+}\text{Fe}_2^{3+}\text{Si}_8\text{O}_{22}(\text{OH})_2$ . Amphiboles exhibit prismatic cleavage, a property of nearly all samples of the amphiboles regardless of habit. There are two cleavage directions, both parallel to the length of the double-silicate chains. Cleavage across

the crystal is usually poor so that the fracture of amphiboles produces long rods or prisms and repeated cleavage produces thinner rods with a rhombic outline consisting of bundles of I beams (i.e.: structural units of the amphibole) (Skinner et al., 1988). The presence of twinning or chain width errors may results in an additional direction of weakness parallel to the length, enhancing the aspect ratio of cleavage fragments (Langer et al., 1991).

#### 4. Properties of asbestiform and non-asbestiform amphiboles

While the chemical compositions of the asbestiform and non-asbestiform amphibole minerals are identical, the characteristics resulting from their differences in crystal habit are significant. The properties of the amphibole asbestos minerals include fibrous habit with parallel fibers occurring in bundles, fiber bundles with split or splayed ends, fibers showing curvature and fibers with high tensile strength. The high tensile strength and axial nature of asbestos means the diameters of asbestos fibrils are largely unaffected by milling. On the other hand, the low tensile strength of non-asbestiform amphiboles means that milling can reduce both particle length and width. The asbestos fibers have good heat insulation qualities, low electrical conductivity, fire resistance, and suitability for weaving. All asbestos minerals separate readily into long flexible fibrils with diameters less than about 0.5  $\mu\text{m}$  and with aspect ratios (length: width ratios) ranging to well over 10,000 (Ross, 1978).

In the hand specimen (that is a sample of the rock as it occurs in nature), the appearance of the non-asbestos minerals is distinctly different from that of the asbestos minerals. This difference persists when viewed by optical and electron microscopy where the non-asbestiform minerals appear as blocks, chunks or slightly elongated particles in contrast to the very evident fibrous nature of asbestos. The non-asbestiform counterparts tend not to grow with parallel alignment. The crystals normally fracture when crushed forming cleavage fragments, some of which may appear as acicular or needle-like crystals because of the way in which amphibole minerals cleave. These cleavage fragments have diameters which on average, are much larger than those of asbestos fibers of the same length. Some asbestiform tremolite fibers with the majority of fiber diameters exceeding 0.25  $\mu\text{m}$ , tested by intra-peritoneal injection in rats were found to be highly carcinogenic (Davis et al., 1991; Lee, 1990). However, almost 70% of the fibers had aspect ratios greater than 10:1, 42% greater than 15:1 and 25% had aspect ratios more than 20:1. This contrasts with the observations that only about 6% of the aspect ratios of cleavage fragments exceed 15:1. The diameters of cleavage fragments appear to be rarely less than 0.25  $\mu\text{m}$  (Table 1).

##### 4.1. Fiber diameters

The aerodynamic behavior of fibers is determined mainly by their diameter (Timbrell, 1982). The majority

Table 1  
The diameters of asbestiform and non-asbestiform amphiboles

"Fiber"	Reference	Percent diameter >0.25 $\mu\text{m}$
Amosite	Gibbs and Hwang (1980)	28–42% (>0.3 $\mu\text{m}$ )
All amphiboles [Homestake Gold mine]	Virta et al. (1983)	100%
Taconite–Grunerite & Actinolite [East Mesabi Range]	Wylie (1988)	100%
Asbestiform tremolite [Swansea]	Lee (1990)	76%
Non-asbestiform tremolite, [Alada Stura, Italy]	Lee (1990)	98%
Non-asbestiform tremolite [Greenland]	Wagner and Berry (1969)	100%
All amphiboles [NY State]	Kelse and Thompson (1989)	100%

of airborne asbestos fibers have diameters less than 0.25  $\mu\text{m}$  making virtually all airborne fibers, respirable. In contrast, only very small percentages of non-asbestiform cleavage fragments have diameters less than 0.25  $\mu\text{m}$  (Table 1).

For the same length distribution, counting fibers by PCM will, based on fiber diameter differences, lead to higher counts of non-asbestiform cleavage fragments than asbestos fibers, because of their visibility by PCM. On the other hand, assuming the same density for fibers as for cleavage fragments, the respirability (i.e. ability of particles to enter the alveolar regions of the lung) of the cleavage fragments will be less than that of asbestos fibers because of their larger diameters. Thus, the PCM method as presently formulated is more stringent for cleavage fragments than for asbestos fibers.

Fiber width is an important parameter determining the potential for causing both lung cancer and mesothelioma. The characteristics of non-asbestiform fiber populations are contrary to the hypothesis of carcinogenicity, while the abundance of thin asbestos fibers supports the hypothesis (Wylie et al., 1993). The evidence from experimental animal studies indicate fibers >1  $\mu\text{m}$  show no dose–response relationship with tumor incidence (<30% of population of non-asbestiform fibers  $\geq 5 \mu\text{m}$  long are <1  $\mu\text{m}$  wide). For fibers <1  $\mu\text{m}$  (and >5  $\mu\text{m}$  long) there is an S-shaped dose–response curve with a threshold and then rapid increase in tumor incidence as the number of thin fibers increases. In populations of asbestos fibers >90% are <1  $\mu\text{m}$  wide and  $\geq 5 \mu\text{m}$  long. Fiber width is also a major factor determining access to the lung. Even long, thin fibers (such as 200  $\mu\text{m}$  long or more) are respirable and are found in lung tissue, while respirability decreases as width increases. Wide diameter cleavage fragments are more likely to be deposited in the upper airways and never gain access to the lower lung to cause disease. The potential for asbestos fiber bundles to disaggregate into increased numbers of even thinner fibers *in vivo* is one of their hazardous features and is not a characteristic of non-asbestiform minerals.

While it has been argued that a major determinant of carcinogenic potential is decreasing fiber width (Wylie et al., 1993), the precise role of the single parameter, diameter in carcinogenesis is still not clear (Addison and McConnell, 2008).

#### 4.2. Fiber length

While the majority of asbestos fibers are in fact short (less than 5  $\mu\text{m}$ ) there are airborne amphibole fibers which exceed 100  $\mu\text{m}$  in length. Complete particle size data (length vs. diameter) on distributions of airborne cleavage fragments and asbestos fibers are extremely limited in number, making it difficult to compare length distribution differences. What data are available indicate that asbestos fibers are longer. For example, Dement et al. (1976) observed that the median length of “fibers” in the airborne dust in the South Dakota Homestake Gold mine was 1.10  $\mu\text{m}$  as seen using scanning electron microscopy. This is less than the median length of airborne grunerite (amosite) asbestos fibers in South Africa mines and mills which were 1.83 and 2.53  $\mu\text{m}$ , respectively (Gibbs and Hwang, 1980) and of grunerite (amosite) asbestos from a pipe insulation operation, 4.9  $\mu\text{m}$  (Dement et al., 1976).

There is other evidence for a clear mineralogical difference between grunerite (amosite) asbestos and grunerite cleavage fragments. Virta et al. (1983) examined airborne particles of grunerite from the Homestake gold mine in South Dakota, particles of cummingtonite, hornblende and actinolite from the Peter Mitchell iron ore pit in Minnesota and particles of grunerite asbestos samples from a shipyard and an electric company. Hornblende is an amphibole that is similar to the tremolite–ferroactinolite series but with aluminum substituted for some of the iron–magnesium as well as for some of the silicon in order to maintain the stoichiometric balance. There were two distinct particle size distributions. The non-asbestiform grunerite distributions from the mining sites were short, wide fibers (average length to width equal to  $4.6 \times 1.1$  and  $5.5 \times 1.2$   $\mu\text{m}$ ). The amosite fibers from the industrial sites were longer and narrower (average length to width equal to  $8.2 \times 0.4$  and  $15.6 \times 0.5$   $\mu\text{m}$ , respectively). Although the populations of grunerite

cleavage fragment and grunerite asbestos are distinct, at the submicroscopic level it may be very difficult to be certain about the specific identity of an individual particle and may be extremely difficult, if not impossible to distinguish asbestos and non-asbestiform particles among the small number of fibers where the two fiber population overlap, especially when the source of the fiber is unknown (Langer et al., 1979).

The New York State talc deposit has been extensively studied for its mineralogy and presence of fibers and cleavage fragments. Commercially important deposits of zinc, lead, talc and wollastonite are found in the Grenville Series of sedimentary rock in St. Lawrence County of NY. Three zinc mines and eleven talc mines have been worked in the area between Balmat Corners and Edwards, NY, which are about eight miles apart. All of these holdings contain some non-asbestiform tremolite, encountered as either a gangue mineral or component of the recovered ore. Anthophyllite and transitional metals have also been identified in variable amounts both between and within mines. We will refer to the NY state talc as St. Lawrence County talc.

Campbell et al. (1979) note that 5–10% of the earth’s crust is amphiboles and therefore many mining industries have amphibole fragments in the gangue mineral tailings. There are at least three habits of non-asbestiform tremolite, none of which have the long, thin fibers characteristic of tremolite asbestos as shown in Table 2.

Long narrow fibers have been shown experimentally to be best capable of inducing mesothelioma when placed directly onto the pleura in experimental animals (Stanton et al., 1981). As there are likely to be fewer long fibers and fewer narrow diameter “fibers” in the case of exposure to amphibole cleavage fragments, compared to asbestos, it would be anticipated that cleavage fragments would pose lower carcinogenic risk.

#### 4.3. Aspect ratios

Asbestos fibers have thin diameters and do not readily break transversely. As a result, length/width ratios can be quite high. All “fibers” will by definition have aspect ratios  $>3:1$ . Around 30% of asbestos fibers will have aspect ratios  $>10:1$  and nearly 20% greater than  $20:1$ .

Table 2

Proportion of tremolite particles longer than 10  $\mu\text{m}$  and narrower than 3  $\mu\text{m}$  from milled blocky (prismatic), acicular, fibrous and tremolite asbestos stratified by aspect ratio using petrographic microscopy<sup>a</sup>

Aspect ratio	% $<3:1$ Non-regulatory	% $3:1$ to $5:1$	% $>5:1$ to $10:1$	% $>10:1$ to $20:1$	% $>20:1$ to $50:1$	% $>50:1$
<i>Non-asbestiform tremolite particles (cleavage fragments)</i>						
Blocky	87	6.5	5	1	0.5	0
Acicular	87	4	6	3	0.5	0
Fibrous	57	18.5	18.5	5.5	0.5	0
<i>Asbestiform tremolite</i>						
Asbestos1	48.5	6.5	13	13.5	13.5	5
Asbestos2	53.5	3.5	14.5	12	13	4.5

Non-regulatory designates particles that do not meet the length  $>5$   $\mu\text{m}$ , width  $<3$   $\mu\text{m}$ , and aspect ratio  $>3$  criteria.

<sup>a</sup> Modified from Table 2 of Campbell et al. (1979).

There were very few cleavage fragments with aspect ratios greater than 10:1. The common blocky variety of non-asbestiform tremolite had less than 2% in the >10:1 class. The acicular and fibrous habits had more particles in the range between 10:1 and 20:1 category than did the blocky variety, but none of the non-asbestiform varieties had more than 0.5% particles in the range between 20:1 and 50:1 and none had any particles >50:1. Nearly 90% of the blocky and acicular habits did not meet the regulatory definition of a fiber. If only fibers that meet regulatory dimensions are counted, 1/100 of non-asbestiform particles have aspect ratios >20:1 while about 35/100 asbestiform tremolite particles have >20:1 aspect ratios (Table 2). A composite aspect ratio distribution reported in the *Pictorial Atlas of Mineral Fibers* (in press) showed that for non-asbestiform particles with an aspect ratio of 3:1 or greater and length greater than 5  $\mu\text{m}$ , 6% on average exceed an aspect ratio of 15:1 and for asbestiform particles, 80% on average exceed an aspect ratio of 15:1. The 3:1 aspect ratio is used principally to eliminate particulates and fiber clumps and improve the precision and accuracy of fiber counts. It is not a defining characteristic of asbestos fibers (Langer et al., 1991).

Wylie et al. (1993) point out that aspect ratio is not a useful parameter for sizing as it is dimensionless, provides no information on width, shows no association with risk of disease, and therefore is of little use in the discussion of risk or exposure.

#### 4.4. Biopersistence

As far as we were able to ascertain, there have been no systematic studies of the biopersistence of cleavage fragments. It is known that for long amphibole asbestos fibers, the half-life is extremely long (Berry, 1999). However, short fibers (i.e.: less than 20  $\mu\text{m}$  in length) can be removed from the lung by macrophage action (Allison, 1973; Bernstein et al., 1994). For later phases of lung clearance, particle solubility is a key factor. In the absence of data, there is no basis for concluding that cleavage fragments will be removed any faster than asbestos fibers during that phase. However, because of their shorter lengths, cleavage fragments are much more likely to be removed more rapidly than amphibole asbestos fibers during the early lung clearance phase. This will reduce their potential for carcinogenic action.

Ilgren (2004) notes dissimilarities that make cleavage fragments much less biopersistent than amphibole asbestos fibers. Surfaces of cleavage fragments have a high density of surface defects, which are preferred sites for dissolution from intracellular acidic enzymes of phagocytic cells that have engulfed them. Amphibole asbestos fibers are smooth and defect free and highly acid resistant. Cleavage fragments are weak, brittle and inflexible because of their weak surface structure, which is further weakened by chemical dissolution. The tensile strength of

amphibole asbestos fibers is 20–115 times greater than the non-asbestiform amphibole variety. This difference becomes greater as width decreases and biological relevance more pronounced. When long, thin biologically relevant cleavage fragments are deposited in the lung alveoli and engulfed by macrophages, the fragment begins to dissolve on all surfaces. They are already weak and inflexible and become thinner and weaker (greater surface area, more surface defects) with increasing susceptibility to chemical dissolution and breakage. The defect-free surface of the amphibole asbestos fiber is better able to resist acid attack. Many of the asbestos fibers are too long to be completely engulfed. Attempts at engulfment produce protein deposits that form an “asbestos body” and eventual death of the cell. In short, biopersistence is a characteristic of carcinogenesis. It is reasonable to conclude that cleavage fragments are likely to be far less bio-persistent than asbestos fibers.

Nolan et al. (1991) compared activity of tremolite cleavage fragments with that of samples of tremolite–actinolite asbestos. For the same surface area, tremolite cleavage fragments had lower ability to alter the permeability of red blood cells than amosite and approximately the same membranolytic activity as anthophyllite and crocidolite. The surface charge of non-asbestos tremolite was about 70% less than asbestos analogues. Schiller et al. (1980) reported that asbestos fibers and cleavage fragments of the same dimensions had the same net negative surface charge. Short fibers and cleavage fragments have a smaller net charge than highly elongated particles.

### 5. Comparison of the risk of health effects in persons exposed to asbestiform and non-asbestiform grunerite

#### 5.1. Grunerite occurrence

Grunerite is the mineralogically correct name for amphiboles of the cummingtonite–grunerite series in which iron is at the 50% point in the 100 times Fe/(Fe + Mg) ratio. Amosite (from the “Asbestos Mines of South Africa”) is the commercial asbestiform product that was used in insulation and building materials. Grunerite asbestos is no longer mined.

The non-asbestiform variety of cummingtonite–grunerite (C–G) has no commercial use *per se* other than as an aggregate but occurs in nature in conjunction with other asbestiform and non-asbestiform amphiboles and other minerals in ore deposits mined for other purposes. In the USA, ore containing C–G has been mined in at least two locations. One location is the Homestake gold mine in Lead, SD, where gold had been extracted since 1876. The other location is Mesabi Range where taconite has been mined since the 1950s and shipped to Silver Bay, Minnesota for extraction of iron. Because of its relationship to grunerite (amosite) asbestos, studies were initiated to determine if these minerals had similar pathogenicity. There have been four cohort studies of

Homestake gold miners (Gilliam et al., 1976; McDonald et al., 1978; Brown et al., 1986; Steenland and Brown, 1995) and two studies of taconite containing amphiboles; one of the Reserve iron deposit (Higgins et al., 1983) and the other of the Erie–Minntac mine (Cooper et al., 1988, 1992) (Table 3).

Taconite iron ore contains actinolite and cummingtonite–grunerite (probably predominantly grunerite). In 1973, elongated grunerite particles, said to be similar to grunerite (amosite) asbestos, were found in the Duluth, Minnesota water supply. The source was mine tailings from the process plant at Silver Bay, Minnesota (MN) serving the Peter Mitchell Pit. In a suit against the Reserve Mining Company, the US Environmental Protection Agency (EPA) claimed that some of the particles were asbestos. This finding initiated a series of studies to determine if there were effects on the Duluth residents (Cook et al., 1974; Masson et al., 1974; Levy et al., 1976; Sigurdson et al., 1981). These studies of human health are not considered further because they are ecological studies without identification of individual exposures or responses, because the route of exposure is via ingestion and because experimental studies and the epidemiological studies described below have provided no evidence in support of any gastrointestinal cancer risk from ingestion. The other health studies are of taconite miners and millers (Clark et al., 1980; Higgins et al., 1983; Cooper et al., 1988, 1992).

A reasonably valid comparison can be made between the health risks of workers exposed to amosite asbestos in mining and manufacture and the health risks of workers involved in the extraction of minerals from ore bodies containing non-asbestiform grunerite.

## 6. Grunerite (amosite) asbestos

Amosite is the trade name given to a mineral that was previously mined in Penge region in the Transvaal of South Africa. The mineralogical name is grunerite asbestos. In the bulk specimen the fibers can be several inches long. The color, ranging grey to brown depends on whether the fiber was mined from a weathered or unweathered zone. The size distribution of the airborne fibers in the mine and mill have been reported by Gibbs and Hwang (1980). In mining and milling 12.6% and 6.6%, respectively, of airborne fibers exceeded 5  $\mu\text{m}$  in length when all particles with length to breadth ratios greater than 3:1 were counted using transmission electron microscopy combined with light optical microscopy. The median lengths for mining and milling were 1.83 and 2.53  $\mu\text{m}$ , respectively. The median diameters were 0.20–0.26  $\mu\text{m}$  depending on the process and there were no airborne fibers with diameters exceeding 3  $\mu\text{m}$ .

### 6.1. Grunerite (amosite) asbestos exposed cohort studies

The studies of cohorts of amosite-exposed workers include miners and millers in South Africa (Sluis-Cremer et al., 1992) and workers engaged in amosite insulation manufacture (Acheson et al., 1984; Seidman et al., 1979, 1986; Levin et al., 1998). Cohorts where the exposure also included riebeckite (crocidolite) asbestos and/or chrysotile have been excluded from consideration as the ratios of the risks of mesothelioma associated with these various asbestos fiber-types have been reported to be in the ratio of 500:100:1 for riebeckite (crocidolite) asbestos, grunerite (amosite) asbestos and chrysotile, respectively (Hodgson and Darnton, 2000). For lung cancer the differences are

Table 3  
Mesothelioma/lung cancer experience—non-asbestiform grunerite<sup>a</sup> Workers and negative non-amphibole controls

Study population	Follow-up period	Cohort <i>N</i> (% dead)	<i>N</i> mesothelioma/ <i>N</i> deaths (PMR)	Lung cancer: <i>O/E</i> = SMR (95% CI)
<i>Non-asbestiform grunerite cohorts (latest follow-up)</i>				
Homestake gold miners (Steenland and Brown, 1995)	Follow-up 1977–1990	3328 (46.6%)	0/1551 = 0 <sup>c</sup>	115/101.8 = 1.13 (0.94–1.36)
Reserve taconite miners (Higgins et al., 1983)	More than 1 year in period 1952–1976	5751 (5.2%)	0/298	15/17.9 = 0.84 (0.47–1.38)
Erie mining of taconite (Cooper et al., 1992)	>3 months <1959, Erie–Minntac mine, 1947–1989	3431 (30.8%)	1 <sup>b</sup> 0/1058 = 0	62/92.2 = 0.67 (0.52–0.86)
Total		12510 (23.2%)	0/2907 = 0	192/211.9 = 0.91
<i>Negative comparison: hematite iron ore without amphiboles</i>				
Hematite mining in Minnesota [Lawler et al., 1985].	>1 year employment before 1966. Follow-up 1937–1979.	Ugd 4708 (55%) Surface 5695 (36%)	0/2642 = 0 0/2057 = 0	117/117.6 = 1.00 (0.83–1.20) 95/108 = 0.88 (0.71–1.08)

<sup>a</sup> It is recognised that these workers were also exposed to non-asbestiform hornblende and actinolite.

<sup>b</sup> Exposure began only 11 years before death making it unlikely that this mesothelioma is related to work in the taconite mine. He was previously a locomotive fireman and engineer.

<sup>c</sup> There were seven cases [four cancers of the peritoneum and three other respiratory cancers] in categories that might include mesothelioma but no mention of mesothelioma on the death certificate or other evidence to support diagnoses of mesothelioma. No mention of mesothelioma was found in a review of deaths from lung cancer or other non-specified cancer, which at times are categories that include mesothelioma (Steenland and Brown, 1995).

not as great or as clear-cut. Crocidolite and amosite pose similar exposure-specific risks for lung cancer (about 5% excess per f/mL years), while the risk from chrysotile is estimated as 0.1–0.5% of the risk of crocidolite and amosite. Thus the risk differentials between the amphibole asbestos (crocidolite and amosite) and chrysotile for lung cancer are about 10–50:1 (Hodgson and Darnton, 2000). It should be noted that the chrysotile in these risk estimates included sources where the chrysotile contained traces of tremolite, the form of which was not investigated or reported.

Only one of the cohorts with pure grunerite (amosite) asbestos exposure was examined for a quantitative exposure–response relationship (Seidman et al., 1986). There was a clear increase in the risk of lung cancer with increasing exposure expressed in fibers/mL years.

## 7. Non-asbestiform grunerite cohorts

Several groups of workers from Homestake gold mine and the Minnesota taconite deposits have been exposed to cleavage fragments of grunerite and studied to assess possible “asbestos-related” diseases (Table 3). The non-asbestiform amphiboles present in these mines generally crystallize in a prismatic habit with well-developed cleavage so breaks occur both perpendicular and parallel to particle length.

### 7.1. Taconite miners

There are several studies of workers who were exposed to cummingtonite–grunerite particles from the above deposits. These include the Reserve taconite miners (Higgins et al., 1983) and the Erie–Minntac taconite miners (Cooper et al., 1988, 1992). Another group of Iron ore (hematite) miners in Minnesota is included for comparison as a negative “control” since the hematite ore does not contain amphiboles (Lawler et al., 1985).

Taconite is an iron-bearing rock that by 1978 was supplying nearly 90% of the iron ore used in the US iron and steel industry. More than 60% of this came from the Mesabi Range that is 110 miles long and 1–3 miles wide extending east to west from Babbitt, Minnesota to Grand Rapids, Michigan. Iron ore has been mined along the Mesabi Range since about 1892 (Langer et al., 1979). Taconite contains 20–50% quartz and 10–36% magnetite with smaller amounts of hematite, carbonates, greenalite, chamosite, minnesotaite, stilpnomelane and amphiboles which are non-asbestiform minerals in the cummingtonite–grunerite series, actinolite and hornblende (Nolan et al., 1999).

Taconite from the eastern end of the Mesabi Range contains non-asbestiform cummingtonite–grunerite (most probably grunerite) and actinolite with most elongated particles having aspect ratios greater than 3:1 and length less than 10  $\mu\text{m}$  and are mostly acicular cleavage fragments. Respirable dust concentrations in the Reserve mining company ranged from about 0.02 to 2.75  $\text{mg}/\text{m}^3$  at a crusher.

The modal range in most jobs was 0.2–0.6  $\text{mg}/\text{m}^3$ , with occasional concentrations of 1–2  $\text{mg}/\text{m}^3$  but mostly below 1  $\text{mg}/\text{m}^3$ . Fiber concentrations were generally <0.5 fibers/mL. Area samples suggest no change in concentrations between 1952 and 1976 and exposure estimates were based on samples collected in the period 1975 and 1958 (Higgins et al., 1983).

In the Reserve mining cohort (Higgins et al., 1983) there were no exposure–response relationships between lung cancer and cumulative exposure to silica dust or taconite (measured as  $\text{mg}/\text{m}^3$  years) and no excess lung cancer based on the SMR. There were no cases of mesothelioma. Higgins et al. (1983) concluded that the lack of any increased risk of cancer is not surprising given the low silica and fiber exposure plus movement of miners to lower exposed jobs with increased seniority. The average and maximum latencies of lung cancer were 15 and 25 years. At high exposure levels the latency for pneumoconiosis has been as short as about 5 years or even less. As dust levels have declined latency is more in the range of 13–20 years. The cohort was also relatively young with 5% overall mortality and the number of cases was small with 15 lung cancer cases (17.9 expected), 8 with >15 years since hire (7.9 expected). Exposure–response functions were estimated using cumulative total dust exposure and cumulative silica dust exposure in  $\text{mg}/\text{m}^3$  years as the exposure metrics. The relationship with total dust exposure, which is of interest from the standpoint of cleavage fragments, was not monotonic and the SMRs were at or below 1.0 in the three highest exposure categories. Higgins et al. (1983) concluded there was no suggestion of an association with lung cancer.

In the Eastern Mesabi district, west of the Reserve Mine are the Erie and Minntac operations. The Minntac ore has had a different metamorphic history and contains the lowest percentage of amphiboles. The Erie ore is a blend of the high and low amphibole ores with more amphiboles than Minntac but less than Reserve. Nolan et al. (1999) reported 28–40% quartz in dust from the Erie mine and 20% quartz from the Minntac mine. Concentrations of fibrous particulates were nearly always <2 fibers/mL. These particulates were >5  $\mu\text{m}$  in length and included elongated cleavage fragments.

The Erie–Minntac cohort of taconite miners (Cooper et al., 1992) showed “no evidence to support any association between low-level exposure to non-asbestiform amphibole particles or quartz” and lung cancer. The Erie–Minntac cohort is older and larger than the Reserve cohort with 31% mortality and a minimum time since hire of 30 years. There were deficits in lung cancer SMRs for miners ever working in high or medium dust areas and no trend with years worked. There was no analysis by cumulative exposure.

There was one case of mesothelioma that had been reported in the initial study (Cooper et al., 1988). In this case, exposure to taconite began 11 years before death. Previous employment included work in the railroad industry as a locomotive fireman and engineer. Nolan et al. (1999)

suggest it is unlikely that the mesothelioma is related to taconite because mesothelioma generally occurs after at least 25 years although latencies as short as about 18 years have been reported among insulation workers where asbestos exposure can be quite high. The more likely cause is from the railroad employment where there are opportunities for exposure to commercial amphibole asbestos from thermal lagging used on steam locomotives. Also, the time since hire in the railroad jobs is more consistent with the long latency characteristic of mesothelioma.

Although deposits of grunerite asbestos large enough for commercial exploitation are very rare, small deposits are occasionally found as a gangue mineral in a limited area of a mine that is otherwise asbestos-free. Nolan et al. (1999) described the occurrence of such a localized seam of grunerite asbestos in a small portion of an iron ore mine otherwise free of asbestos. Samples from the seam revealed three kinds of morphological types or habits. One kind was the asbestiform habit with fibers occurring as parallel fibrils and forming polyfilamentous bundles. There were two non-asbestiform habits, namely splintery fibers and massive anhedral nodules, which when crushed may form elongated cleavage fragments that morphologically resemble some asbestiform fibers. To evaluate potential asbestos exposure, 179 personal air samples were collected for all relevant jobs associated with work on this localized seam. The mean concentration of fibers  $\geq 5 \mu\text{m}$  in length and aspect ratio  $\geq 3:1$  was 0.05 f/mL and the highest was 0.39 f/mL. All sample results were below the Mine Safety and Health Administration (MSHA) standard of 2 f/mL but 13% were above the Occupational Safety and Health Administration (OSHA) standard of 0.1 f/mL.

Nolan et al. (1999) estimated the potential lifetime risk of lung cancer and mesothelioma based on a worst case scenario. Lifetime lung cancer risks of 0.1 and 0.6/100,000 for non-smokers and smokers respectively were estimated using the EPA risk model and assuming a linear exposure–response relationship, age of 45 years at beginning of exposure and continuous exposure for 22 days to 0.05 asbestos fibers/mL. This was considered approximately equivalent to smoking 2 or 12 cigarettes over a lifetime.

Nolan et al. (1999) also estimated risk based on grunerite asbestos fiber content in the lungs of mesothelioma cases from a British grunerite (amosite) asbestos factory (Gibbs et al., 1994). Nolan et al. (1999) estimated it would take 75–265 years of daily 8-h shifts to inhale the number of fibers found in the lungs of the mesothelioma cases, assuming no clearance. Fiber concentrations were about 45% higher in the lung cancer cases, suggesting about 100–380 years to reach similar fiber content in iron ore miner lungs.

Nolan et al. (1999) suggested concentrations were a minimum of 30 fibers/mL in the Paterson, NJ grunerite (amosite) asbestos factory (Seidman et al., 1986). No mesothelioma cases had less than 6 months employment and 20-years latency. Assuming breathing 0.05 fibers/mL from the gangue rock in the iron ore mine, Nolan et al.

(1999) estimated it would take about 300 years to achieve the minimum exposures estimated for the mesothelioma cases in the Seidman et al. (1986) cohort.

## 7.2. Hematite miners as negative control

Hematite from the Mesabi Range in Minnesota is a mixture of about 83% hematite ( $\text{Fe}_2\text{O}_3$ ) and limonite ( $\text{HFeO}_2$ ). The hematite deposit differs from taconite deposits in that there is the absence of all amphiboles. Some silica (about 8%) is present plus possibly low levels of radon.

Lung cancer mortality was not associated with years worked. Mesothelioma was not mentioned. Lawler et al. (1985) considered that the lack of an excess risk of respiratory disease was possibly due to strict prohibition of smoking while underground, apparent absence of significant radon daughter exposure and/or the aggressive silicosis control program. No estimates of dust exposure are available.

## 7.3. Gold miners

There are several studies of miners at the Homestake gold mine in South Dakota (Gilliam et al., 1976; McDonald et al., 1978; Brown et al., 1986; Steenland and Brown, 1995).

Ore containing cummingtonite–grunerite has been mined to extract gold in Lead, South Dakota, since 1876. An analysis of airborne “fibers” using electron diffraction and X-ray spectrometry was reported to show that it contained “80–90% amphiboles” with the amphiboles being “60–70% fibrous grunerite”, “1–2% fibrous cummingtonite” and “10–15% fibrous hornblende” (Gilliam et al., 1976). The free silica content of the respirable airborne dust was reported to be 13.1%. Low concentrations of arsenopyrite were also reported. The NIOSH researchers identified the fibrous grunerite as grunerite (amosite) asbestos. Closer examination of the fiber population statistics suggests strongly that the fibrous grunerite particles are non-asbestos amphibole cleavage fragments as noted in the section on fiber length.

Measurements of airborne concentrations of “fibers” in the mine in 1974 showed concentrations to be about 0.25 f/mL greater than  $5 \mu\text{m}$  with the highest concentration being 2.8 f/mL based on 200 samples (Gilliam et al., 1976). The mean total fiber concentration in the mine as determined by electron microscopy was 4.82 ( $\pm 0.68$ ) f/mL with the concentration of fibers greater than  $5 \mu\text{m}$  being 0.36 ( $\pm 0.08$ ) f/mL. Approximately 94% of fibers were less than  $5 \mu\text{m}$  in length, the mean fiber diameter was 0.13  $\mu\text{m}$  and the mean “fiber” length was 1.1  $\mu\text{m}$ . The US Bureau of Mines in 1960 reported average airborne dust concentrations of 1.7 million particles per cubic foot (mppcf) (Gilliam et al., 1976). This suggests a ratio of f/mL to mppcf of about  $0.25/1.7 = 0.146 \text{ f/mL per } 1 \text{ mppcf}$ .

Exposure–response relationships were developed by several of these researchers. Only the results of the latest follow-up by Steenland and Brown (1995) will be consid-

ered. However, the exposure–response developed by McDonald et al. (1978) based on semi-quantitative exposure estimates is of interest because this cohort of 1321 men with 21 or more years of service clearly had adequate latency to observe the occurrence of mesothelioma or increase in lung cancer. There were 17 deaths from respiratory cancer but no convincing evidence of an excess of respiratory cancer or grunerite related mesothelioma. This contrasts with the results of the earlier study by Gilliam et al. (1976), which involved 440 men who had worked more than 5 years underground. They reported 10 deaths from neoplasms of the respiratory system with 2.7 deaths expected. Conclusions from the study by Gilliam et al. (1976) are weakened by the fact that the study population is small, the SMR for men with latency less than 20 years (5.4) was greater than that for men with latency greater than 20 years (3.2) (McDonald et al., 1978), and the results are contradictory to later follow-up studies of the entire cohort (Brown et al., 1986; Steenland and Brown, 1995). While the reason for the high overall SMRs is not clear, selection bias is possible as the cohort was comprised of volunteers participating in a 1960 silica X-ray survey. The participation rate of workers from the mine was not reported.

The Homestake study comprises the largest and oldest cohort of workers exposed to non-asbestiform amphiboles with 47% mortality. In the Steenland and Brown (1995) study, there was a 2.6-fold excess of silicosis and a 3.5-fold excess of respiratory TB that were significantly associated with cumulative exposure and SMRs were significantly elevated in the highest exposure category for both dust-related diseases. Lung cancer was not associated with cumulative exposure in the SMR exposure–response analysis and there was a negative trend in the nested lung cancer case–control portion of this study, i.e., as exposure increased there was a trend for lung cancer risk to decrease. There were no mesothelioma deaths.

The mesothelioma and lung cancer experience of the grunerite (amosite) asbestos and non-fibrous amphibole workers will be compared separately below.

## 8. Comparison of mesothelioma experience

One method of assessing whether non-asbestiform grunerite acts similarly to grunerite (amosite) asbestos is to compare the proportional mortality from mesothelioma in grunerite (amosite) asbestos exposed workers and in non-asbestiform grunerite exposed workers. Mesothelioma is a cancer which can clearly be caused by amosite without known confounders such as smoking, although there are a small number of other potential causes (Pelmar, 1988; Price and Ware, 2004). Hodgson and Darnton (2000) argue that there is unlikely to be a threshold for asbestos-related mesothelioma, but that the exposure–response function may be non-linear. As previously discussed about 80% of mesotheliomas are asbestos related, mesothelioma is a more specific indicator of amphibole asbestos exposure

and also more sensitive as there may be an excess mesothelioma risk in the absence of an excess lung cancer risk (Hodgson and Darnton, 2000).

The measure of mesothelioma mortality used in this study is the percent of total mortality (labelled PMR in this context). To assume a work-related mesothelioma in the non-asbestiform grunerite cohorts there should be no previous asbestos exposure, no exposure to other potential etiological factors such as erionite or therapeutic radiation and the time of death should probably be 20 or more years since hire, or 15 or more years since hire if exposure was intense. Lanphear and Buncher (1992) estimated that for 1105 mesothelioma cases meeting strict histological and exposure criteria, 99% had a latent period (time since first exposure) of 15 years or more and 96% of 20 years or more. The median latent period was 32 years with a range of 13–70 years. The probability was 0% for <10 years and 0.45% for 10–14 years.

Although there were only 19% of persons dead in the grunerite (amosite) asbestos cohorts combined, there was an overall proportional mortality from mesothelioma of 1.2%. In contrast, 23% of persons were dead in the non-asbestiform cohorts combined and no mesothelioma linked to the exposures in the non-asbestiform cohorts (or 0.03% if the non-exposure related deaths are counted). It is well recognized that the proportion of mesothelioma increases with long follow-up as mesothelioma increases as a cubed function of the time since first exposure and so would increase as the percentage of deaths increase. Certainly on present evidence there is no increased risk of mesothelioma in non-asbestiform amphibole exposed workers at the levels of exposure encountered in these industries (Tables 3 and 4 and Fig. 1).

In view of the fact that there was no detected increase in mesothelioma, one would not anticipate an increased risk of lung cancer due to exposure to fibrous dust, as usually in amphibole-exposed workers the exposure necessary to produce an increased risk of lung cancer is much greater than that required to increase mesothelioma risk.

## 9. Comparison of lung cancer experience

There are statistically significant excesses of respiratory cancer in all the grunerite (amosite) asbestos industries (except mining). In contrast, it is very clear that, with the exception of the first small study of Homestake gold miners (Gilliam et al., 1976), there is no increased risk of lung cancer in the non-asbestiform amphibole exposed industries. The results from the study by Gilliam have not been reproduced in subsequent studies with complete ascertainment of the cohort and longer follow-up (Steenland and Brown, 1995; McDonald et al., 1978). In the taconite-exposed miners there were some statistically significant deficits of respiratory cancer. This is in spite of the fact that workers in those industries are exposed to significant crystalline silica in addition to non-asbestiform grunerite (if silica increases lung cancer risk).

Table 4  
Mesothelioma/lung cancer experience–grunerite (amosite) asbestos exposed workers

Study population	Follow-up period	No. in cohort (% mortality)	No. meso/No. deaths = PMR	Lung cancer: obs/ exp = SMR (95% CI)
Amosite mining (Sluis-Cremer et al., 1992)	Miners 1945–1955. Follow-up to 1986	3212 (20.2%)	4/648 = 0.6%	26/18.8 = 1.38 (0.97–1.91)
Amosite Insulation manufacturing (Acheson et al., 1984)	1945–1978; Follow-up to 1980.	4820 (6.9%)	5/333 = 1.5%	61/29.1 = 2.10 (1.62–2.71)
Amosite insulation manufacturing (Seidman et al., 1986; follow-up of Seidman et al., 1979)	1941–1945; more than 5-year latency; follow-up to 1983	820 (72%)	6/593 = 1.01% (death certificates) 17/593 = 2.9% (best evidence)	102/20.51 = 4.97 (4.08–6.1)
Amosite insulation manufacturing (Levin et al., 1998)	1954–1972, >10 years latency; follow-up to 1994	755 (29.4%)	6/222 = 2.7%	35/12.6 = 2.77 (1.93–3.85)
Total		9607 (18.7 %)	21/1796 = 1.2%	224/81 = 2.77

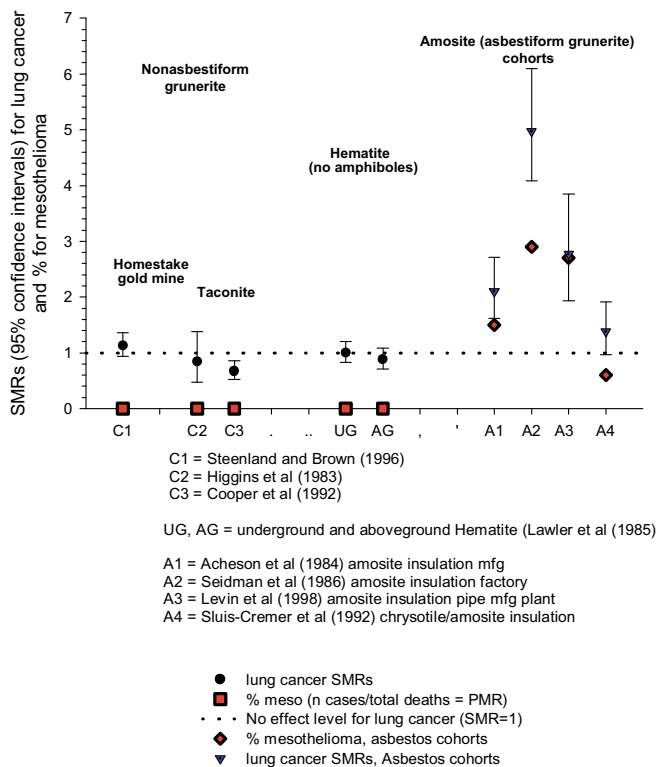


Fig. 1. Lung cancer and mesothelioma mortality in cohorts of workers exposed to non-asbestiform amphiboles (Homestake gold ore, taconite), hematite (no amphiboles, negative controls) and amosite asbestos cohorts of insulation factories and miners (positive controls).

Table 5  
Lung cancer SMRs by cumulative exposure expressed as fiber/ml years for non-asbestiform grunerite [Steenland and Brown, 1995] and asbestiform grunerite exposures [Seidman et al., 1986]

Non-asbestiform grunerite [Steenland and Brown, 1995]								
mppcf-years <sup>a</sup>	<33.3	33.3–133.3	133.3–200	>200	—	—	—	—
Fiber/mL years <sup>b</sup>	<4.8	4.8–19.5	19.5–29.2	>29.2				
SMR	1.17	1.01	0.97	1.31				
Asbestiform grunerite [Seidman et al., 1986]								
Fiber/mL years <sup>b</sup>	<6	6–11.9	12–24.9	25–49.9	50–99.9	100–149.9	150–249.9	250+
SMR	14/5.31 = 2.64	12/2.89 = 4.15	15/3.39 = 4.42	12/2.78 = 4.32	17/2.38 = 7.14	9/1.49 = 6.04	12/1.32 = 9.09	11/.94 = 11.7

<sup>a</sup> Dust days in Table 2 of the paper by Steenland and Brown (1995) (i.e.: 1 day at 1 mppcf was converted to dust years by dividing by 240 days per year [i.e. 48 weeks × 5 day week]).

<sup>b</sup> mppcf years converted to f/cc-years using a factor of 1 mppcf = 0.146 f/mL. The conversion is based on the average concentration of “fibers” greater than 5 μm and particles measured by the midjet impinger and reported by Gilliam et al. (1976) i.e.: 0.25 f/mL divided by 1.7 mppcf.

Another way to examine this question is to compare the exposure–response relationships for the various studies. In Table 5 the exposure–response relationships for the studies by Seidman et al. (1986) and Steenland and Brown (1995) are compared. While both have limitations in their exposure estimates, there is clearly no increasing trend of lung cancer with increasing exposure to non-asbestiform grunerite (and other non-asbestiform amphiboles). The exponential increase in pneumoconiosis (silicosis) with increasing exposure suggests exposure produced fibrotic but not carcinogenic effects (ratio lung cancer/ silicosis mortality = 1.25). In contrast there is a steep and statistically significant slope for the lung cancer mortality in the grunerite (amosite) asbestos insulation manufacturing plant (lung cancer/asbestosis mortality ratio = 6.8) (Fig. 2).

Acheson et al. (1984) reported concentrations of 30 fibers/mL in the late 1960s in the factory using grunerite (amosite) asbestos. Exposures were probably much dustier before 1964 with improved conditions after 1964. However, Acheson et al. (1984) did not attempt to assess exposure–response trends.

It seems clear that exposure to non-asbestiform grunerite cleavage fragments and/or “fibers” at cumulative exposures below about 30 f/mL years has not resulted in an increased lung cancer risk for workers. The risk for workers exposed to grunerite (amosite) asbestos was increased at cumulative exposures <6 f/mL years.

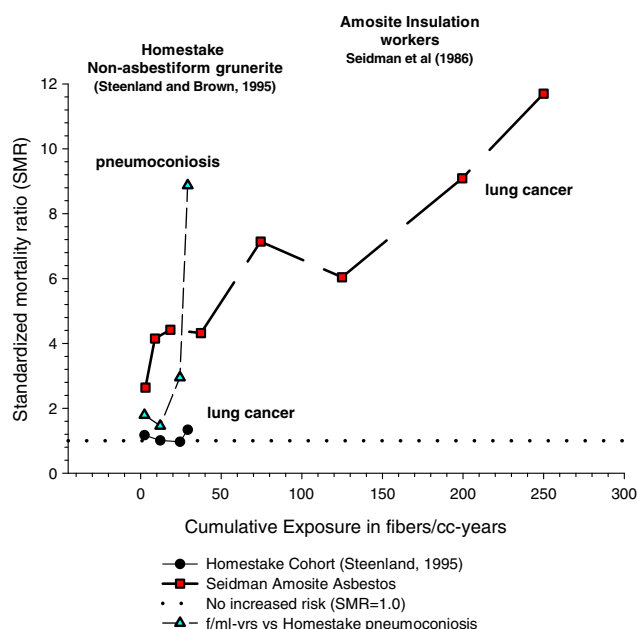


Fig. 2. Lung cancer SMRs by cumulative exposure (fibers/mL years) and pneumoconiosis for non-asbestiform grunerite (Steenland and Brown, 1995) and grunerite (amosite) asbestos (Seidman et al., 1986).

## 10. Overall conclusion concerning asbestiform and non-asbestiform grunerite

It is evident that the “fibers” to which the non-asbestiform amphibole workers were exposed were considerably shorter (and wider) than those to which grunerite (amosite) asbestos workers were exposed. While both studies of grunerite (amosite) asbestos and non-asbestiform grunerite (plus other non-asbestiform amphiboles) may have limitations as far as estimates of fiber exposure are concerned, the results indicate very large differences in the mortality from mesothelioma and from lung cancer from both external and internal comparisons. It seems unlikely that errors in the exposure estimates are responsible for these very large differences as the grunerite (amosite) asbestos factory shows a definite increase in risk of lung cancer with increasing exposure while there is no statistically valid increase in trend with non-asbestiform grunerite. The results are consistent with cleavage fragments having no (or negligible or very low) apparent carcinogenic hazard for mesothelioma and lung cancer in contrast to the obvious carcinogenic hazard shown by their asbestiform counterparts.

## 11. The evidence from studies of talc and vermiculite exposed workers

### 11.1. The mineral talc

The term talc is used in two ways. First, it is a term applied to a commercial or industrial product that contains finely divided mineral or rock powder that usually, but not always contains the mineral talc as its main component.

Second, it can refer to the mineral talc which is a phyllosilicate mineral with the chemical formula  $\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})_2$ . Since talc is a metamorphic mineral it is often associated with other minerals and is rarely found in its pure form. Co-exposures are specific to each site. Tremolitic talc is a commercial product that contains a high proportion of the amphibole tremolite in addition to the mineral talc; it also can contain other minerals including anthophyllite, a transitional talc/anthophyllite mineral as well as antigorite, lizardite and quartz. Cosmetic and pharmaceutical talcs have strictly controlled mineral contents; industrial talcs may contain other minerals.

Structurally, talc occurs in sheets that can be separated by slight pressure, so that when milled, talc can form cleavage fragments or elongated talc platelets (Wild et al., 2002).

## 12. The New York and Norwegian talc deposits

There are at least two talc deposits containing non-asbestiform tremolite and anthophyllite which have been studied, one in New York State and one in Norway (Table 6). The best known and best characterised is the industrial talc in New York. There has been considerable discussion in the literature concerning whether the tremolite and anthophyllite present in this talc is asbestiform or non-asbestiform. However, the evidence is supportive of non-asbestiform amphiboles (Skinner et al., 1988). Norwegian talc contains tremolite and anthophyllite said to be in trace amounts. However, the mineralogy of this talc is less studied and the cohort of exposed miners/millers is much smaller.

The health experience (mesothelioma and lung cancer mortality) of these two cohorts of talc workers exposed to non-asbestiform amphiboles will be compared to (1) anthophyllite asbestos miners, (2) to workers exposed to vermiculite contaminated with tremolite asbestos; and (3) to workers exposed to talc that is not contaminated with amphiboles from Vermont, Italy, France and Austria.

### 12.1. New York talc

The St. Lawrence County, New York talc deposit has been extensively studied for its mineralogy and presence of fibers and cleavage fragments. The mineralogy is complex and there has been a long and ongoing debate about the amphiboles present in the Gouverneur, NY talc, which is the only mine currently operating in the region. Dement et al. (1980) concluded that bulk Gouverneur talc samples contained both amphiboles (4.5–15% anthophyllite and 37–59% tremolite) and serpentines (10–15% lizardite and antigorite) and less than 2.6% free silica as determined by X-ray diffraction and petrographic microscope analysis. It appears that the mineral identified as anthophyllite by Dement et al. (1980), is, at least in part, a mixed phase mineral with talc evolving from the anthophyllite (Kelse and Thompson, 1989). The talc also contains talc fibers. Dement et al. (1980) considered the airborne dust ‘fibers’

Table 6  
Lung cancer and nonmalignant respiratory disease (NMRD) mortality (SMR) among talc workers

Author	Years	Lung cancer SMR	Lung cancer mine SMR	Lung cancer mill SMR	NMRD overall SMR	NMRD mine SMR	NMRD mill SMR	Mesothelioma
NY, Brown et al. (1979)	1947–1959 Follow-up 1975 19% mortality	9/3.3 = 2.73 (1.25–5.18)			8/2.9 = 2.76 (1.19–5.13)  Other 5/1.3 = 3.85 (1.25–8.96)			0
NY, Lamm et al. (1988)	1947–1978 >1-year tenure 14.8% mortality	6/3.1 = 1.93 (0.71–4.20)			7/2.5 = 2.78 (1.11–5.72)			
NY, Honda et al. (2002)	>1 day tenure 1948–1989	31/13 = 2.32 (1.57–3.29)	18/46 = 3.94 (2.33–6.22)	7/5.5 = 1.28 (0.51–2.63)	28/13 = 2.21 (1.47–3.20)	10/4.2 = 2.41 (1.16–4.44)		0
NY, Brown et al. (1990)	1947–1978; follow-up 1983; 23% mortality ≥1-year tenure	17/8.2 = 2.07 (1.20–3.31) 9/4.7 = 1.91 (0.88–3.64)			17/6.8 = 2.50 (1.46–4.01)  11/3.8 = 2.89 (1.45–5.18)			0
Vermont, Selevan et al. (1979)	1940–1975; >1-year tenure before 1970; 23% mortality	6/3.69 = 1.63 (0.60–3.54)	5/1.15 = 4.35 (1.41–10.1)	2/1.96 = 1.02 (0.12–3.68)	11/3.67 = 3.0 (1.50–5.36)  Other = 11/1.79 = 6.15 (3.07–11)	2/1.23 = 1.63 (0.20–5.87)  Other = 2/ 0.56 = (0.43–2.89)	7/1.72 = 4.07  Other = 7/ 0.89 = 7.87 (3.15–16.2)	0
Italy, Coggiola et al. (2003)	>1 year, 1946–1995 49% mortality	44/ 46.9 = 0.94 (0.68–1.26)	33/ 30.9 = 1.07 (0.73–1.50)	11/ 16 = 0.69 (0.34–1.23)	127/55.7 = 2.28 (1.9–2.72)	105/34.4 = 3.05 (2.5–3.7)	22/21.3 = 1.04 (0.65–1.57)	
France, Wild et al. (2002)	1945–1995, >1-year; 27.5% mortality	21/17 = 1.23 (0.76–1.89)			26/24.6 = 1.06 (0.69–1.55) Pneumoconiosis 3/0.5 = 5.56 (1.12–16.2)			
Austria, Wild et al. (2002)	1972–1996, >1-year; 12.4% mortality	7/6.6 = 1.06 (0.43–2.19)			1/3.7 = 0.27 (0.01–1.52)			0
Norway, Wergeland et al. (1990)	>1-yr: miners 1944–1972; 28.7% mortality >2-years millers 1935–1972; 30.5% mortality	SIR: 6/ 6.49 = 0.92 (0.34–2.01)	SIR: 2/ 1.27 = 1.57 (0.19–5.69)	SIR: 4/ 5.22 = 0.77 (0.21–1.96)	Diseases of Respiratory System SMR: 3/10.9 = 0.28 (0.06–0.80)	SMR: 1/ 2.5 = 0.40 (0.01–2.23)	SMR: 2 / 8.5 = 0.24 (0.03–0.85)	0

greater than 5  $\mu\text{m}$  long to contain upward of 70% amphibole asbestos. Based on electron microscopy, Dement and Zumwalde reported that: “In the mine 38% of all fibers were anthophyllite. 19% were tremolite and 39% were unidentified”. In the mill 45 per cent of all fibers were anthophyllite, 12 per cent were tremolite and 38 per cent were unidentified. Three percent of the fibers in the mine and 2 percent in the mill reportedly gave chrysotile electron diffraction patterns. According to Thompson (1984) and Harvey (1979) all the amphibole minerals are cleavage fragments and in the non-asbestiform habit and it has now been shown that once the talc fibers are recognized, the talc does not contain asbestiform tremolite or asbestiform anthophyllite (Kelse and Thompson, 1989; Dunn Geoscience Corp., 1985; Langer and Nolan, 1989; Virta, 1985; Crane, 1986; Wylie et al., 1987; Wylie et al., 1993; Nolan et al., 1991).

A survey of the many mortality studies of workers exposed to St. Lawrence County, NY talc is summarised in Appendix A. Most of these have been variations of the original NIOSH cohort study (Brown et al., 1979; Dement et al., 1980). We will focus on the nested case-control study, which addressed three of the hypotheses raised about reasons for the increased lung cancer, namely smoking, other work exposures, and short-term workers (Gamble, 1993). Honda et al. (2002) added six more years update and estimated quantitative cumulative exposure to talc dust to address the question of exposure-response (Oestenstad et al., 2002).

Gamble (1993) conducted a case-control study nested in the Brown et al. (1990) cohort of NY talc workers. There were 22 cases and 66 controls matched on date of birth and date of hire. All cases were either smokers (91%) or ex-smokers compared to 27% non-smokers, 73% smokers or exsmokers among controls. Negative trends were consistently observed by years worked after controlling for smoking, 20 or more years latency, and exclusion of short-term workers. Lifetime work histories suggested no apparent association with non-talc exposures or non-Gouverneur talc exposures. The author concluded that “after adjustment for...smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure”. The time occurrence of lung cancer was consistent with a smoking etiology, and was not consistent with a mineral dust relationship.

Honda et al. (2002) assessed cancer and non-cancer mortality among white male Gouverneur talc workers. The cohort analyzed for cancer endpoints consisted of 809 workers employed 1947–1989 and alive in 1950. The cohort analyzed for non-cancer endpoints consisted of 782 men employed during 1960–1989. The important additions in this study were 6 more years of follow-up (through 1989) and internal exposure-response analyses with cumulative exposure to talc dust as the exposure variable. Smoking status was not taken into account. The internal comparisons by cumulative exposure ( $\text{mg}/\text{m}^3$  years)

showed a significant monotonic decrease in lung cancer risk with increasing exposure. The RR was 0.5 (0.2–1.3) in the highest exposure category. Mortality from ‘other NMRD’ and pulmonary fibrosis showed monotonic increases in risk as exposure increased with 2- and 12-fold increased risks in the highest exposure categories (Fig. 3).

Honda et al. (2002) concluded that talc dust was unlikely to have a carcinogenic potency similar to asbestos for several reasons. First, there were negative exposure-response trends. Second, although lung cancer mortality was increased nearly 4-fold among miners (SMR of 3.94; 95% CI 2.33–6.22, 18 observed (obs)) it was not excessive among millers (SMR of 1.28; 95% CI 0.51–2.63; 7 obs) although exposure was similar in both groups (medians of 739 and 683  $\text{mg}/\text{m}^3$  years, respectively). Third, the cumulative exposure was low for lung cancer cases compared to that of other workers. For example, if median cumulative exposure is set at 1.0 for lung cancer decedents, the relative median cumulative exposure is 1.1 for ischemic heart disease, 1.5 for all decedents, 3.5 for NMRD as underlying or contributory cause of death, and 10.8 for pulmonary fibrosis.

Honda et al. (2002) conclude that the lung cancer excess is unlikely to be due to talc dust *per se*. The reasons for the excess are unclear. Possible explanations for the excess include confounding by smoking or other risk factors or an unidentified constituent in the ore or mine environment that is poorly correlated with talc dust.

## 12.2. Norwegian talc

Norwegian talc contains trace amounts of quartz, tremolite and anthophyllite; the main minerals are talc and

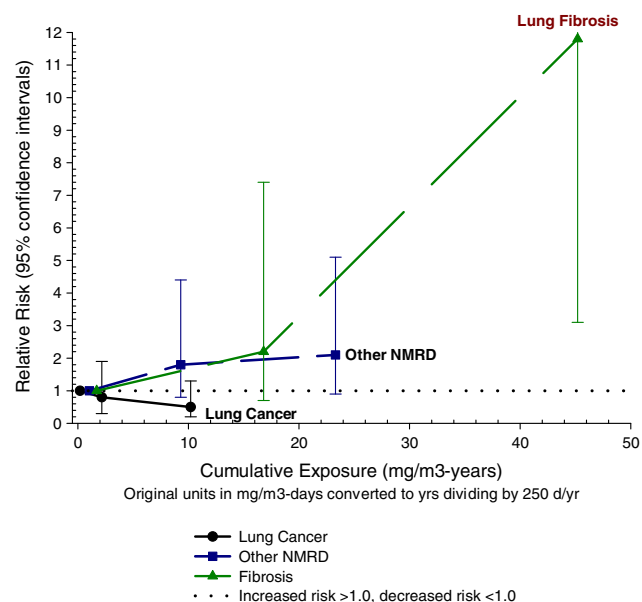


Fig. 3. Exposure-response of lung cancer, other non-malignant respiratory disease (other NMRD) and lung fibrosis by cumulative exposure ( $\text{mg}/\text{m}^3$  years) Honda et al. (2002).

magnesite. Small amounts of magnetite, chromite, chlorite, and antigorite are in the ore, while the surrounding rock contains small amounts of serpentine, mica, feldspar, calcite, and non-asbestiform amphiboles (hornblende, tremolite). Personal air samples were collected 1982–1984. Exposures were somewhat higher in the mine with a range for total dust of 0.94–97.4 mg/m<sup>3</sup> and peaks at drilling of 319 mg/m<sup>3</sup>. The range in the mill was 1.4–54.1 mg/m<sup>3</sup> with peaks in the storehouse of 109 mg/m<sup>3</sup>. Fibers of tremolite, anthophyllite and talc with aspect ratios >3:1 by optical microscopy ranged from 0.2 to 0.9 f/mL (Wergeland et al., 1990).

The Norwegian male talc cohort consisted of 94 miners employed at least 1 year in talc-exposed jobs 1944–1972 and 295 millers employed at least 2 years 1935–1972 (Wergeland et al., 1990). In contrast to NY talc workers, this is a generally healthy work population with a significant deficit in all-cause mortality (SMR of 0.75; 0.62–0.89), which was below expected in both mine and mill. There were only 6 incident cases of lung cancer and 6.49 expected for an SIR of 0.92. There was a small positive trend with years worked because there were zero cases in the low tenure group but no significant excess (SIR) in the two groups with longer tenure. There were two lung cancer cases among miners (1.27 expected) and there were more expected (5.22) than observed (4) in the mill. There was no excess of NMRD cases (three cases of pneumonia), but numbers were too small to make any conclusions. There were no cases of mesothelioma.

It is unclear why the mortality and incidence of cancer are so far below expected. There is no excess NMRD mortality and no cases of pneumoconiosis as a cause of death despite the apparently very high dust exposures. There were three cases of pneumoconiosis as a contributing cause of death: two cases with silicosis, one case with talcosis. In 1981, smoking histories were obtained from 63 of 94 miners. A reduced prevalence of smoking is an unlikely cause of the reduced mortality as only 8% were non-smokers. In view of the small size of this cohort, interpretation is difficult.

### 13. Non-asbestiform amphiboles in South Carolina vermiculite

There are several small vermiculite pits in South Carolina containing nearly 50% tremolite/actinolite but is believed to be virtually free of fibrous tremolite (McDonald et al., 1988). Mining and the first part of the milling process are carried out wet. Four types of elongated fibers were identified in air samples using analytical transmission EM and energy dispersive X-ray spectroscopy (EDSX): tremolite–actinolite (48%), vermiculite fragments (8%), talc/anthophyllite (5%), iron-rich fibers (23%) and the rest unidentified. Mean fiber size was 1.1 µm diameter and 12.7 µm long. Mean fiber length seems to be quite large for the airborne fibrous dust cloud to be totally cleavage fragments. The mean expo-

sure was 0.75 f/mL years. Nolan et al. (1991) found tremolite cleavage fragments (some of which were >10:1 aspect ratio), but found no asbestos.

The mortality study comprises a small cohort of 194 men with 6 months or more tenure before 1971 and a minimum latency of 15 years. There were 51 total deaths and an all-cause mortality of 1.17 (0.87–1.51). There were four deaths from lung cancer and three from NMRD with SMRs of 1.21 and 1.22, respectively. There were no cases of mesothelioma and no deaths from pneumoconiosis. There was a negative exposure–response trend between cumulative fiber exposure and lung cancer (Fig. 4). Three of the four cases were in the lowest exposure category of <1 f/mL years (SMR = 1.71) and the 4th case was in the medium exposure category of 1–10 f/mL years (SMR = 0.73). Given the low fiber exposures (mean 0.75 f/mL years) and the small sample size the authors concluded there was inadequate power to detect an adverse effect in this population (McDonald et al., 1988).

The health experience of workers at this mine would be of considerable interest for comparison with the miners in Montana where exposures involve asbestiform “tremolite” and other fibers. Exposure levels were so much higher in Montana and the study population is so small and exposures so low in South Carolina that comparisons are difficult. In the longer term, the population is too small for confident conclusions concerning lack of risk. On the other hand, the exposure–response trends (Fig. 4) are suggestive that if tremolite asbestos were present instead of cleavage fragments there would likely have been an increase in lung cancer in the highest exposure category (and the work envi-

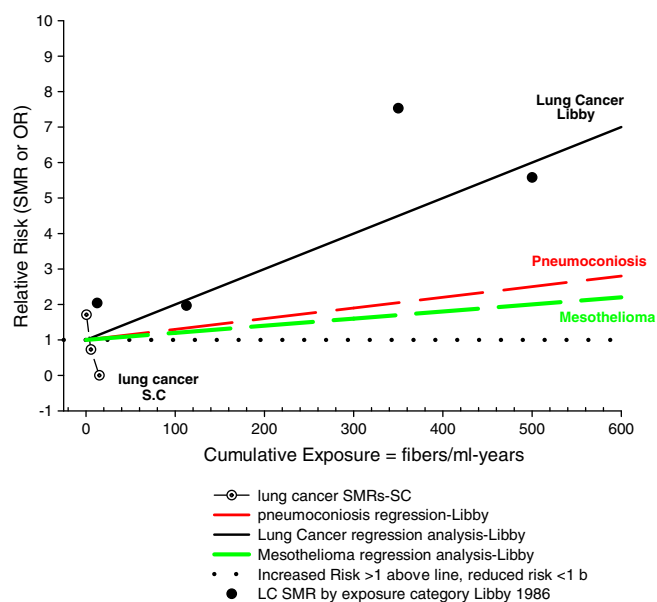


Fig. 4. Exposure–response trends for lung cancer, mesothelioma and Pneumoconiosis among Vermiculite workers exposed to Vermiculite Ore contaminated with tremolite asbestos in Libby, Montana (McDonald et al., 1986a,b) Vermiculite with non-asbestiform amphiboles in South Carolina (McDonald et al., 1988).

ronment would have been more dusty with higher exposures).

Although the actual percentage of “non-asbestiform” anthophyllite in the airborne dust is not clear in these studies, we will assume that the airborne dust contains a proportion of non-asbestiform anthophyllite and non-asbestiform tremolite. In view of this, comparison of the risk of mesothelioma and lung cancer in the NY and Norwegian talc mining industry will be compared with other talc studies (negative control) and with asbestos-exposed workers in anthophyllite mining and workers exposed to vermiculite contaminated with tremolite asbestos (positive comparison). South Carolina vermiculite will be compared with Libby, Montana vermiculite.

#### 14. Other talc deposits

There are several mortality studies of talc where amphibole minerals are reported to be absent and the talc is relatively “pure” talc. These include studies of workers in the Vermont talc mines (Selevan et al., 1979), Italian talc mines (Coggiola et al., 2003), French and Austrian talc mines (Wild et al., 2002) (Table 6). According to Wild et al. (2002) “no asbestos contamination has ever been clearly documented in the talc deposits, at least not in the European sites”.

#### 15. Lung cancer in New York and Vermont talc miners and millers

In contrast to the high levels of amphibole cleavage fragments in New York’s St. Lawrence County talcs, geological studies conducted since the early 1900s have shown no “asbestos” and little quartz in Vermont talc deposits (Boundy et al., 1979). Analyses of bulk samples collected in 1975/1976 from mines and mills of the three major Vermont talc companies showed talc and magnesite as major components (20–100%) and chlorite and/or dolomite as minor constituents (5–20%). There were trace amounts (<5%) of dolomite, calcite, quartz, biotite, ankerite, chromite, phlogopite and oligoclase and no asbestos.

Sampling surveys conducted in summer/winter of 1975/1976 at the three talc mines/mills resulted in respirable geometric mean concentrations in the mines ranging from 0.5 to 5.1 mg/m<sup>3</sup> (median = 0.9) and in the mills from 0.5 to 2.9 mg/m<sup>3</sup> (median = 1.0). Two methods were used to count “fibers” with aspect ratios  $\geq 3:1$  and a “maximum width and minimum length” of 5  $\mu\text{m}$ . Counts using phase contrast microscopy at a magnification of 437 $\times$  ranged from 0 to 60 fibers/mL (median = 4.1). Parallel fibers counted by SEM at a magnification of 5000 $\times$  ranged from 0 to 0.8 fibers/mL (median = 0). Cumulative exposures were not estimated, but past exposure levels commonly exceeded the MSHA and OSHA standards of 20 mppcf (Selevan et al., 1979).

The Vermont talc study provides the best comparison with the New York talc because the original studies were

conducted during the same time period using similar methods and some of the same investigators, and the mines were in adjacent US States (although different ore bodies).

The cohort comprised 392 men who had had a chest radiograph administered by the Vermont Health Department since 1937 and had been employed for more than 1 year in the Vermont talc industry between January 1, 1940 and December 31, 1969. Workers were followed through December 31, 1975. As the inclusion of workers in the cohort required a radiographic examination, it was thought that long-term workers were more likely to have participated than short-term workers. In the 1960s the Health Department reported that 70% of those missing from their radiographic surveys had less than 1-year employment. While the overall effect is not known, the original authors concluded that selection bias could not explain the observed excess mortality.

There were a total of 90 deaths with an overall SMR of 1.16. There was a six-fold excess mortality (11 obs, 1.79 exp) from NMRD (excluding influenza and pneumonia). The largest excess was among millers (7 obs, SMR = 7.87), but mortality was also increased among miners (2 obs, SMR = 3.6). Radiographic evidence of pneumoconiosis (80% > category 2/1) taken as part of the annual radiographic surveillance program of active workers, suggested to the authors that Vermont talc exposure was the causal agent. There was a non-significant 1.63-fold overall excess of lung cancer, which was significant among the miners (5 obs, SMR = 4.35) but not millers (2 obs, SMR = 1.02). There were no cases of mesothelioma (Selevan et al., 1979).

The most similar cohorts are Brown et al. (1979, 1980) and Lamm et al. (1988) (Table 6). Lamm et al. (1988) considered workers with >1 year tenure, which can be compared to Vermont. Brown et al. (1979, 1980) included all workers irrespective of tenure.

Risks of lung cancer were similar in Vermont and the NY talc workers with 1 or more year employment (1.63 versus 1.93, respectively) but elevated to 2.7 when all workers are included. The SMR for lung cancer among NY talc workers with less than 1-year tenure was 3.17 (6 obs) (Lamm et al., 1988). This supports the conclusion of Lamm et al. (1988) that the risk of lung cancer in NY talc workers is concentrated in short-term workers and is most likely due to risks acquired elsewhere.

Risks of NMRD were increased 3-fold in all three cohorts. Risk of pneumoconiosis appeared to be higher in Vermont as non-infectious respiratory disease mortality (possible surrogate for pneumoconiosis) was increased 6-fold compared to about 4-fold for both studies of NY talc workers.

In the Vermont mills the mortality from NMRD was twice that in the mines. However, the risk of lung cancer was four times greater in the mine than mill. Exposures in both mine and mill in Vermont were above the then standard of 20 mppcf, but cumulative exposures were thought to be higher in the mill than the mine because mine opera-

tions were more sporadic. Selevan et al. (1979) concluded that for NMRD, “additional etiologic agent(s) either alone or in combination with talc dust affect mine workers” because exposures were higher in the mill than in the mines yet mortality was higher in the mines. If this same reasoning is used for lung cancer, one would also conclude that other etiological agents were involved since SMRs for lung cancer were near the null among millers in both Vermont (Selevan et al., 1979) and the updated NY talc cohort (Honda et al., 2002) (Table 6).

A clear limitation of the Vermont study is the small number of deaths; there were only six lung cancer deaths and 11 deaths from NMRD. Nevertheless, the increased risk of lung cancer in talc miners in Vermont where there is no evidence of exposure to asbestos or amphibole cleavage fragments is consistent with a conclusion that amphibole cleavage fragments are not responsible for the increased risk of lung cancer in the New York Talc miners. On the other hand the increased risk of Non-Malignant Respiratory Disease (Pneumoconiosis) appears to be related to both Vermont and NY talc dust exposure. Further follow-up and quantitative exposure–response analysis of the NY talc cohort tested these hypotheses and found that cumulative exposure to talc dust showed a strong association with pulmonary fibrosis mortality, a moderate association with other NMRD and no association with lung cancer (Honda et al., 2002; Oestenstad et al., 2002).

It is informative to think about the history of these two cohorts of similar size and similar risks and hopefully learn some useful lessons. There has been no further follow-up of the Vermont talc cohort. The NY cohort has been re-analyzed several times both with and without further follow-up (Stille and Tabershaw, 1982; Lamm et al., 1988; Brown et al., 1990; Gamble, 1993; Oestenstad et al., 2002; Honda et al., 2002). From the earlier studies has come the common (and current) perception that talc in the Gouverneur Talc District contains asbestos and that “exposures to asbestiform tremolite and anthophyllite stand out as the prime suspected etiologic factors associated with the observed increase in bronchogenic cancer” (Brown et al., 1980). We offer two possible reasons for this incorrect perception.

First is the difference between including and not including short-term employees. The evidence that lung cancer risk was concentrated in short-term workers appears to have been outweighed by the known risks associated with asbestos and the presumption that NY talc workers were exposed to talc containing asbestos. The excess lung cancer among Vermont talc miners appears to have been discounted due to “talc free both of asbestiform minerals and significant quantities of free silica” and the potential for additional etiologic agents either alone or in combination with talc dust (e.g., radon).

Second, the most important limitation is with regard to the asbestos standard for regulating asbestos minerals. The OSHA–NIOSH definition of asbestos is inadequate for identifying and regulating non-asbestiform amphiboles. The crushing of rock containing non-asbestiform amphiboles

(and other minerals) produces cleavage fragments that conform to the OSHA–NIOSH definition of asbestos (e.g.,  $\geq 3:1$  aspect ratio,  $\geq 5 \mu\text{m}$  length) but are not asbestos fibers.

Using this definition has produced errors regarding asbestos content of the ores that are the subject of this review, i.e., taconite tailings dumped into Lake Superior (see other presentations in this volume), asbestos exposure of Homestake gold miners (Gilliam et al., 1976) as well as talc. Other examples of the potential misuse of the federal fiber definition for asbestos include allegations of asbestos in play sand (Langer et al., 1991) and in crayons. The Agency for Toxic Substances and Disease Registry (ATSDR) in their Public Health Statement for Asbestos suggest that talc may contain asbestos. The Australian Government National Occupational and Health Commission say that industrial talc generally contains “asbestos fibers, notably tremolite”. By this standard one might include all the negative control talc cohorts as positive controls of workers exposed to asbestiform amphiboles. More examples are readily available on the internet. While amphiboles are sometimes present in some talc, asbestiform amphiboles occur very rarely as a geological curiosity and not as far as we are aware using a mineralogical definition in any commercial or industrial talc.

The reasons for the increased risks of lung cancer in the New York and Vermont mining areas still remain speculative. Exposure to radon may be one reason as levels were apparently elevated in the Vermont Mines. The possibility that miners worked in areas of high asbestiform tremolite in the past cannot be totally excluded on present evidence as in one closed mine in Vermont “cobblestones of serpentine rock which were “highly tremolitic” have been reported, although workers in the Vermont cohort were considered unlikely to have had such exposure (Selevan et al., 1979). Whether this was asbestiform tremolite is not described although this appears to be inferred.

## 16. Italian talc

Italian talc is very pure and is used in the pharmaceutical and cosmetic industries. Miners and millers in this industry were studied for mortality (Rubino et al., 1976, 1979; Coggiola et al., 2003). Miners were analyzed separately from millers because of silica exposure in the mine. The silica content of airborne dust in the mines was as high as 18% in drilling operations from footwall contact rocks, rock type inclusions, and carbonate, calcite and magnesite inclusions. The quartz content of the rock strata was inconsistent, ranging from 10% to 45%. Other minerals in the inclusions included muscovite, chlorite, garnet, and some carbonate material. A small amount of (non-asbestiform?) tremolite was detected in the inclusions but not in the talc samples. Talc samples were commonly contaminated with chlorite. From 1920 to 1950 there was dry drilling and no forced ventilation so exposures were over 10 times the TLV (which appears to have been about 25 mppcf at that time) in the mines and a little

over the TLV in the mills. Wet drilling and forced ventilation were introduced in about 1950 and dust concentrations dropped precipitously to about 1 mppcf and well below the TLV. Concentrations in the mills were reduced slightly and slowly and after about 1960 were higher than in the mines (Rubino et al., 1976).

Coggiola et al. (2003) updated the earlier talc studies by Rubino et al. (1976, 1979). The updated cohort comprised 1795 men with at least 1 year of employment 1946–1995 and national rates were used for comparisons. There were 880 observed deaths with an overall SMR of 1.20 (1.12–1.28). There were slight deficits in observed lung cancer and total cancer and there were no mesotheliomas.

The SMR for lung cancer was 1.07 (0.73–1.50) for miners, while there was a deficit of lung cancer with an SMR of 0.69 (0.34–1.23) in millers. There was a 2-fold excess of NMRD due mainly to silicosis with the excess occurring among miners with a significant SMR of 3.05 (2.50–3.70) compared to 1.04 (0.65–1.57) among millers. Exposure–response was examined using duration of exposure. This showed that for miners the only lung cancer excess was in the <10-year exposure group while for NMRD the exposure–response trends were flat with all categories of duration of exposure showing about a 2-fold excess mortality.

The authors concluded there was no association between lung cancer or mesothelioma and exposure to talc containing no asbestos fibers. But there was an association in miners between NMRD (primarily silicosis) and talc containing quartz.

## 17. French and Austrian tales

Wild et al. (2002) conducted cohort studies of talc workers in France and Austria with nested case–control studies of lung cancer and NMRD. The French ore was a talc chlorite mixture with quartz contamination ranging from undetectable to less than 3%. In Austria, three mines were studied. At one site the ore was a talc–chlorite mixture with 0.5–4% quartz. Rock containing about 25% gneiss was not milled. A talc–dolomite mixture of 25% medium talc and <1% quartz in the final product was the product at the second mine. The ore at the third site did not contain talc but was mixture of approximately equal proportions of quartz, chlorite and mica. Workers were stratified into semi-quantitative exposure categories. The non-exposed group consisted of office workers not exposed to talc and personal dust samples averaged 0.2 mg/m<sup>3</sup>. The low exposure group was for workers with no direct contact to talc, such as maintenance workers, and concentrations were less than 5 mg/m<sup>3</sup>. The medium exposure category included workers exposed to concentrations between 5 and 30 mg/m<sup>3</sup> for dustier areas such as bagging or milling and onsite maintenance. Quartz exposures occurred mostly in underground mining, tunneling and barrage building and milling products at site D. The highest exposure category was reserved for past production jobs (all before 1980) where concentrations were >30 mg/m<sup>3</sup>. Some samples produced concentra-

tions >50 mg/m<sup>3</sup> and higher. Three samples taken on workers wearing personal protective equipment were 73, 82 and 159 mg/m<sup>3</sup>. To calculate cumulative exposures, values of 2.5, 10 and 40 mg/m<sup>3</sup> were assigned to the low, medium and high exposure jobs.

The French cohort consisted of 1070 men with more than one year tenure between 1945 and 1995, with vital status follow-up through 1996. The Austrian cohort consisted of 542 men with >1-year tenure between 1972 through 1995 and vital status follow-up during this same period. Three controls per each case of NMRD and lung cancer from both the French and Austrian cohorts were matched on age and calendar year of employment.

Overall mortality was below expected. There were 294 deaths in the French cohort in the period 1968–1996 for an SMR of 0.93 (0.82–1.04). The Austrian cohort was smaller with 67 deaths and an SMR of 0.75 (0.58–0.95). In the French cohort SMRs were only slightly elevated for NMRD and lung cancer (1.06 and 1.23, respectively) but were increased over five-fold (SMR 5.56 CI 1.12–16.2) for the three cases with pneumoconiosis. There were zero mesotheliomas.

The case–control studies combined the French and Austrian cohorts. There were 40 combined deaths from NMRD: 10 from pneumoconiosis (including silicotuberculosis), 10 from chronic obstructive pulmonary disease (COPD, restricted to chronic bronchitis and airway obstruction), and 20 deaths from pneumonia and other diseases. When analyzed by exposure categories, the exposure–response trend for NMRD was not monotonic, with no apparent increased mortality below 400 mg/m<sup>3</sup> years and 2-, and 2.5-fold increased risks in the two highest exposure categories respectively. When analyzed by conditional logistic regression there was a significant exposure–response trend with an 8% increased risk per 100 mg/m<sup>3</sup> years exposure. The slope was even higher for pneumoconiosis, 1.17 for pneumoconiosis versus 1.08 for NMRD. The slope was only 1.02 for COPD. Adjustments for covariates in the regression analyses had little effect on these trends. Smoking prevalences were similar between cases and controls with about 40% non-smokers (Fig. 5).

There were 30 combined lung cancer cases. There was a negative exposure–response trend with odds ratios of 0.6 and 0.73 in the two highest exposure categories. The trend was unchanged when adjustments were made for smoking, quartz, working underground or when lagging the exposure estimates. Also, there were no trends when analyzed by maximum dose, latency, or duration of exposure (data not shown). About 40% of the controls were non-smokers compared to about 8% (1/19) among cases although smoking classification was unknown on about half of the cases.

Wild et al. (2002) concluded that the small excess of lung cancer was not due to talc, despite follow-up of over 50 years, high exposures and mean duration of exposure >20 years.

The pattern of mortality of workers exposed to cleavage fragments in the New York talc mines and mills (Fig. 3) is

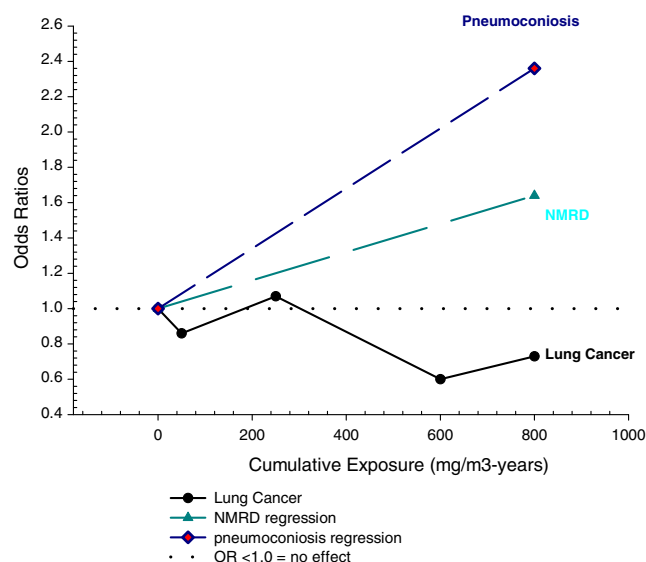


Fig. 5. Exposure-response trends for lung cancer Non-malignant respiratory disease (NMRD) and Pneumoconiosis by cumulative exposure (mg/m<sup>3</sup> years) to Talc not containing amphiboles Among French & Austrian Talc Workers Wild et al. (2002).

very similar to that of workers in the French and Austrian mines and mills where there was no exposure to cleavage fragments (Fig. 5). A limitation in these comparisons is the very large differences in cumulative exposures. If they are comparable, the dust to which the New York miners and millers are exposed is considerably more potent than that in the French and Austrian mines and mills from the standpoint of increasing lung fibrosis/pneumoconiosis. On the other hand, this “apparently highly potent pneumoconiosis producing dust” does not increase lung cancer risk.

These studies show that “pure” talc does not increase lung cancer risk. This is consistent with the observations for the New York millers, exposed to talc as there was no excess lung cancer in talc millers.

## 18. Asbestos-exposed cohorts for comparison with talc workers

There are two ore deposits containing tremolite asbestos or anthophyllite asbestos potentially suitable for comparison with the talc cohorts exposed to non-asbestiform tremolite and asbestos. One site is the vermiculite mine located in Libby, Montana with significant contamination from tremolite asbestos. The other is an anthophyllite asbestos mine in Finland.

### 18.1. Libby, Montana vermiculite mine contaminated with asbestiform amphibole

Ore fed to the mill in Libby, Montana contains 4–6% asbestiform amphiboles (about half tremolite asbestos and the other half a mixture of winchite and richterite in

the tremolitic series, Nolan et al., 1991). The health concern is the asbestiform amphibole contamination in these ores and not the vermiculite itself.

The raw ore and vermiculite concentrate from the Libby mine contain both asbestiform and non-asbestiform tremolite-actinolite and non-fibrous anthophyllite. Atkinson et al. (1982) found 21–26% fibrous tremolite-actinolite in the raw ore and 2–6% in the concentrate. Company data taken several years later indicated 3.5–6.4% at the head feed of the mill and 0.4–1% in the concentrate (Amandus et al., 1987a). After removal of coarse rock the ore contained about 20% vermiculite, 21–26% fibrous tremolite-actinolite and the rest augite, biotite, calcite, diopside, hornblende, magnetite, quartz, sphene, and apparently non-fibrous tremolite-actinolite (McDonald et al., 1986a,b).

Eight airborne samples from the mill and screening plant examined by phase contrast light microscopy indicated the asbestiform nature of the particles: 96% had aspect ratios >10, 67% >20 and 16% >50. In addition, 73% of the fibers were longer than 10 μm, 36% >20 μm and 11% >40 μm and width was <2.5 μm in all instances (Amandus et al., 1987a).

Two independent mortality studies of the Montana vermiculite have been conducted. McDonald et al. (1986a,b) conducted a radiological survey and a cohort and nested case-control study of 406 persons employed for at least a year prior to 1963 with follow-up until 1983. The cohort study was subsequently updated with follow-up to 1999 (McDonald et al., 2002, 2004). We will primarily focus on the up-dated analysis. Exposure was estimated from first exposure (1945) to 1982 when work histories were no longer available. By this date most of the cohort was no longer employed and fiber concentrations were about 0.1 f/mL. The plant closed in 1990. Before wet milling processes were installed, fiber concentrations were very high (estimates of >100 f/mL). A wet mill was installed in 1955 and an entirely wet process replaced both wet and dry mills in 1974 so by 1980 nearly all concentrations were <1 f/mL. Exposure-response was estimated by both categorical and linear exposure-response (E-R) Poisson regression models and excluding those with <10 years latency. Average and cumulative exposure metrics showed similar relationships with mortality (Table 7).

The overall all cause SMR was 1.27 (1.13–1.43). SMRs for lung cancer and NMRD were 2.40 (1.74–3.22) and 3.09 (2.30–4.06), respectively; the PMR for mesothelioma was 4.2%. Exposure-response trends were not linear, as risks of lung cancer, NMRD and mesothelioma increased steeply in the second quartile exposure category and showed less steep slopes in the third and fourth exposure quartiles (Fig. 4 and Table 7).

The other Libby cohort study was by NIOSH and published in 3 sections that included exposure estimates (Amandus et al., 1987a), cohort mortality study (Amandus and Wheeler, 1987b) and a cross-sectional radiographic study (Amandus et al., 1987c). Amandus and Wheeler

Table 7

Mesothelioma/lung cancer experience—non-asbestiform anthophyllite and anthophyllite asbestos miners and tremolite asbestos

Study population	Follow-up period	N in cohort (% deaths)	PMR (mesothelioma/total deaths)	Lung cancer SMR (95% confidence intervals)
Talc workers, NY State, <a href="#">Honda et al. (2002)</a>	White men actively employed >1 day between 1948 and 1989 and alive in or after 1950. Follow-up 1950 thru 1989	809 (27%) Mill = 377 Mine = 311	2/209 = 0.96% <sup>a</sup>	31/13 = 2.32 (1.57–3.29) Mill: 7/5.5 = 1.28 (0.51–2.63) Mine: 18/4.6 = 3.94 (2.33–6.22)
Norwegian talc workers, <a href="#">Wergeland et al. (1990)</a>	Miners >1 year 1944–1972; Millers >2 years 1935–1972; Follow-up 1953–1987	Total (M) 389 (30.1%) 94 miners (28.7%) 295 millers (30.5%)	0/117 = 0% 0/ 27 = 0% 0/ 90 = 0%	Incidence (SIR): 6/6.49 = 0.92 (0.34–2.01) 2/1.27 = 1.57 4/ 5.22 = 0.77
Finnish anthophyllite asbestos miners, <a href="#">Karjalainen et al. (1994)</a> , <a href="#">Meurman et al. (1994)</a>	>3 months 1953–1967; Follow-up 1953–1991	999 (59.4%) M = 736 (68.3%) F = 167 (53.9%)	4/593 (0.7%) M = 4/503 (0.8%) F = 0/90 (0%)	Incidence: SIR M: 76/26.4 = 2.88 (2.27–3.6) Heavy Exp: 3.15 (2.37–4.09) Mod Exp: 2.35 (1.45–3.58)
Vermiculite miners, Libby, MN, <a href="#">McDonald et al. (2004)</a>	>1 year before 1963, followed to 1999	406 70.2% mortality	12/285 = 4.2%	44/18.3 = 2.40 (1.74–3.22)
South Carolina Vermiculite, <a href="#">McDonald et al. (1988)</a>	<6 months 1971–1986, followed to 1986 (>15 years latency)	194 51/194 = 27.8%	0/51 = 0%	4/3.31 = 1.21 (0.33–3.09)

<sup>a</sup> See text. Cases were not considered to have resulted from work at the talc mine. One case had latency of 15 years and one was a draftsman during construction only.

Table 8

Dimensions of elongated particles associated with various amphibole exposure industries studied experimentally and/or epidemiologically

Cohort	Width (μm)	Length (μm)	Reference
Libby vermiculite; tremolite asbestos	46%, <0.25	62%, >5	<a href="#">Langer et al. (1974)</a>
Homestake gold mine (CG = cummingtonite–grunerite) (TA = tremolite–actinolite) (GM = geometric mean)	69% CG: GM = 0.43 15% TA: GM = 0.27 0%, <0.25 minimum 0.3 mean 1.1	34%, >5; 32%, >5 Mean 4.6; Max 17.5	<a href="#">Brown et al. (1986)</a> <a href="#">Virta et al. (1983)</a>
Taconite	0%, <0.25 min 0.25 mean 1.2	Mean 5.5; Max 32.4	<a href="#">Wylie (1988)</a>
Vanderbilt tremolitic talc	0%, <0.25		<a href="#">Kelse and Thompson (1989)</a>
Experimental studies			
Korean tremolite asbestos >5 μm L	44.7%, <0.25	11.8%, >5 [1.9]	<a href="#">Addison (2004)</a> , <a href="#">Davis et al. (1985)</a>
Californian white tremolite asbestos ( <a href="#">Davis et al., 1991</a> )	50%, <0.25	14.9%, >5 [3.2]	<a href="#">Addison (2004)</a>
Swansea tremolite asbestos ( <a href="#">Davis et al., 1991</a> )	8.2%, <0.25	33.6%, >5 [1.0]	<a href="#">Addison (2004)</a>
Italian tremolite ( <a href="#">Davis et al., 1991</a> )	13.3%, <0.25	9.7%, >5 [0.27]	<a href="#">Addison (2004)</a>
Greenland tremolite, <a href="#">Wagner et al. (1982)</a>	0%, <0.25	100%, <10	<a href="#">Wagner and Berry (1969)</a> , <a href="#">Wagner et al. (1982)</a>
Dornie, Scotland tremolite, <a href="#">Davis et al. (1991)</a>	13.7%, <0.25	22.5%, >5 [0.1]	<a href="#">Addison (2004)</a>
Shinness tremolite, <a href="#">Davis et al. (1991)</a>	13.8%, <0.25	10.6%, >5 [0]	<a href="#">Addison (2004)</a>
Ferro-actinolite asbestos	Median: 0.24, range: 0.03–5.2	Median: 1.50, range: 0.3–52.5	<a href="#">Coffin et al. (1982)</a>
UICC Amosite	Median: 0.22, range: 0.02–4.1	Median: 1.8, range: 0.15–378	<a href="#">Coffin et al. (1982)</a>

Figures in □ = % >5 μm and less than 0.25 μm. [Addison \(2004\)](#) provided figures from [Davis et al. \(1991\)](#), calculated from the fiber numbers in the doses used in the experiments by [Davis et al.](#)

(1987b) also reported positive exposure–response trends for lung cancer with an almost 7-fold increased SMR in the high exposure category with more than 20-years latency. The PMR for mesothelioma was 2.2% considering only those with 20 years or more latency.

These results are a marked contrast to the decreasing trend of lung cancer with increasing exposure seen in the St. Lawrence, NY talc workers. There is little doubt that the mesothelioma experience of the Montana work force is considerably worse than that of the talc miners. This is

in spite of the fact that the New York talc workers are reported to have been exposed to dusts containing a very high percentage of non-asbestiform amphibole fibers (Kelse and Thompson, 1989).

The amphiboles in St. Lawrence, NY talc are non-asbestiform while they are asbestos in the Libby deposit (Kelse and Thompson, 1989; Langer and Nolan, 1989; Thompson, 1984; Dement et al., 1980).

Risk of pneumoconiosis, lung cancer and mesothelioma clearly increase as cumulative exposure to asbestiform tremolite increases (Fig. 4). For the talc workers exposed to non-asbestiform tremolite, the risk of NMRD and pneumoconiosis increase as exposure increases, but the trends are reversed for lung cancer (inverse trend) and for mesothelioma (no cases so there is no trend) (Fig. 3).

### 18.2. Finnish anthophyllite asbestos miners/millers

Dement et al. (1980) mentioned the study of Finnish miners by Meurman et al. (1974) in the belief that both the NY talc and Finnish anthophyllite asbestos cohorts were exposed to asbestiform anthophyllite. They recommended that the risk of mesothelioma should be further studied by further follow-up of the NY talc workers. Both the NY talc (Honda et al., 2002) and anthophyllite asbestos cohorts have had further follow-up so the maximum latency in Finland is now about 40 years (Karjalainen et al., 1994; Meurman et al., 1994), which is about the same as for NY talc workers (Honda et al., 2002).

In the updated Finnish study there was a significant 2.9-fold excess incidence of lung cancer overall with a somewhat higher risk in the heavily exposed males (SIR 3.15) than in moderately exposed (SIR 2.35). There were four mesothelioma cases for a significant 46-fold increased SIR (95% CI = 12.2–115) overall (or a PMR of 0.7%, 4/593). All of the cases were in the heavy exposure group where there was a 67-fold excess (95% CI = 18.3–172) and all four had asbestosis. Asbestosis was mentioned on 20% of all death certificates (Karjalainen et al., 1994; Meurman et al., 1994).

### 18.3. Mesothelioma comparison

In the NY talc cohort, Honda et al. (2002) reported two deaths from mesothelioma. One was coded as benign neoplasm of the respiratory system and the other as malignant neoplasm of the lung and bronchus, unspecified. One man worked for 15 years and died 15 years after starting work at the talc facility. He had been a carpenter and millwright for 16 years, 8 years as a lead miner and 5 years as a repairman in a milk plant. The other man worked briefly at the facility as a draftsman during mill construction in 1947–8. He would have had minimal talc exposure. He had been employed on the construction of a previous talc mine, and then installed oil burning heating systems. Honda et al. (2002) concluded it is unlikely that either of these cases occurred as a result of talc exposure in the mine or mill.

In essence, there are no mesothelioma cases that are plausibly related to occupational exposure to Gouverneur talc.

Vianna et al. (1981) reported a mesothelioma rate in Jefferson County twice that of New York State based on an incidence study of histologically confirmed mesothelioma cases. A total of six cases, four male and two female cases diagnosed between 1973 and 1978 were reported to have occurred in talc miners. Enterline and Henderson (1987) reported an excess mesothelioma incidence in Jefferson County from 1968 to 1981 with 4 female (0.6 expected) cases and 7 male (1.4 expected) cases for risk ratios of 6.7 and 5.0, respectively. These latter rates were the second and sixth highest in the USA and occur in the county next to the one where the talc mines are located.

Hull et al. (2002) drew attention to these elevated rates, added “five new mesothelioma cases,” and concluded that New York talc exposure was associated with an increased risk of mesothelioma. This conclusion is inconsistent with the limited available data as outlined in the following:

- The entire work histories of the “talc miners” with mesothelioma are apparently not known. Exposure to asbestos in other jobs is likely given the diagnosis of asbestosis and the smaller widths of the fibers in lung tissue.
- Hull et al. (2002) attempt to interpret the results of their tissue analyses based on only two mesothelioma cases. This sample is too limited to reach any reliable conclusions. Available data do not support a talc etiology.
- Fiber dimensions are consistent with asbestos exposure as the mean fiber widths in the two mesothelioma cases examined are less than 0.25  $\mu\text{m}$ , which are the dimensions characteristic of asbestos.
- The source of the fibers in the lungs is unlikely to be NY talc mines. The average width of the fibers in the mesothelioma lungs was 0.15  $\mu\text{m}$ , which is considerably less than the average width of 1.3  $\mu\text{m}$  of anthophyllite and tremolite in milled talc samples (Siegrist and Wylie, 1980). Kelse and Thompson (1989) reported that 0% of the fibers in NY talc samples had widths less than 0.25  $\mu\text{m}$ .
- Asbestos-related employment occurs among residents of both St. Lawrence and Jefferson counties. Fitzgerald et al. (1991) reported that 39% of workers with radiographic abnormalities of parenchyma and pleura had been employed for a year or more in asbestos-related industries (e.g., shipyard, construction, pipe and furnace insulation).
- Two of the five cases had worked only 4 and 2 years in occupations likely to be linked to the mining industry. One of these persons died at age 72 and the other at age 53. There was no information concerning their employment during the rest of their lives.
- A non-talc etiology for mesothelioma is plausible. As noted above, females in the talc mining counties have a greater risk of mesothelioma than males (Enterline

and Henderson, 1987). On the other hand, the cohort data on talc workers is based on men because less than 5% of those hired in the talc industry were women (Honda et al., 2002; Brown et al., 1990; Lamm et al., 1988).

- In the cohorts, the worker populations and exposures are well defined and no association is observed between talc or non-asbestiform amphibole exposure and mesothelioma in the absence of possible asbestos exposure. The cohort studies provide a more reliable estimate of risk than a small case report with limited information on exposure.
- Hull et al. (2002) indicate the “increased pleural mesothelioma mortality [is] in Jefferson County”. Jefferson County stopped producing talc about 100 years ago and all talc over the past century has been mined in St. Lawrence County.
- In the Libby cohort there were twelve mesothelioma cases. The PMR was 4.2 %. Exposure to tremolite asbestos in the Libby vermiculite clearly increased the risk of mesothelioma significantly (McDonald et al., 2004). The risk of mesothelioma among anthophyllite asbestos workers was less than the risk among crocidolite miners but almost as great as among amosite miners (Meurman et al., 1994). These comparisons show a clear excess incidence of mesothelioma for workers exposed to asbestiform tremolite and anthophyllite, but no mesothelioma attributable to exposure to non-asbestiform tremolite/actinolite or anthophyllite. These comparisons are graphically displayed in Fig. 6.

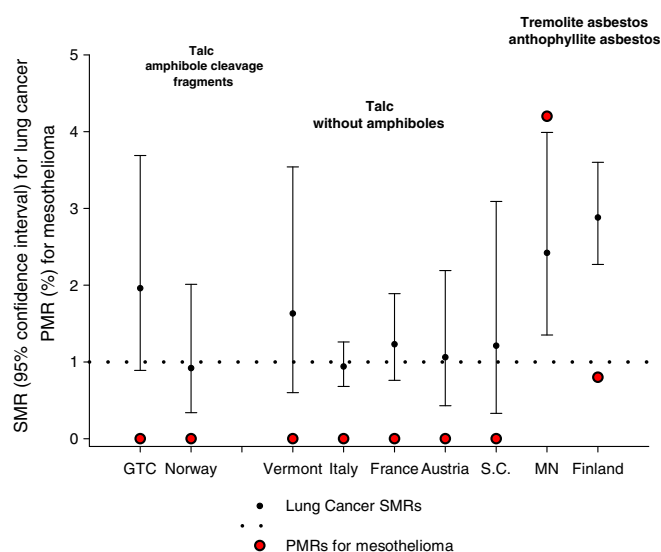


Fig. 6. Lung cancer and mesothelioma mortality in workers exposed to Talc containing non-asbestiform amphiboles in New York and Norway (Honda et al., 2002, Wergeland et al. (1990) Talc without amphiboles (Vermont, Italy, France/Austria) Selevan et al. (1979), Coggiola et al. (2003), Wild et al. (2002) and Vermiculite containing tremolite asbestos McDonald et al., 1986a,b Anthophyllite Asbestos (Karjalainen et al., 1994; Meurman et al., 1994).

#### 18.4. Lung cancer comparison

There was an overall 2-fold increased rate of lung cancer in the Gouverneur talc miners and millers compared to the surrounding counties in which the mine was located. This excess of lung cancer was not associated with dust exposure but was concentrated in miners with an SMR of 3.94 (CI 3.33–6.22) while millers had only a small increased risk with an SMR of 1.28 (CI 0.51–2.63). In contrast, non-malignant respiratory disease mortality was associated with dust exposure as it was increased in both miners (SMR 2.41, CI 1.16–4.44) and in millers (SMR 2.27 CI 1.13–4.07) to almost the same extent. Smoking was clearly a confounding exposure as 100% of cases were smokers or ex-smokers but only 73% among controls. When exposure–response relationships were examined, the rate ratio for the highest respirable dust exposed workers to the lowest respirable dust exposed workers was 0.5 (0.2–1.3) for lung cancer and 11.8 (3.1–44.9) for pulmonary fibrosis (Fig. 3). One would expect that a respirable dust exposure index would reflect the respirable fractions of dust regardless of composition. Thus, the results indicate that the lung cancer excess in this industry is largely due to smoking and unlikely to be the result of exposure to the respirable fraction of dust (which would include talc and cleavage fragments of the various amphibole minerals). However the data suggest that the respirable dust did increase the risk of fibrosis.

In asbestos producing or using industries where midget impinger measurements were used as a basis for exposure estimates (Liddell et al., 1997), the risk of lung cancer increased with increasing levels of exposure. This illustrates the validity of exposure indices based on midget impinger measurements for assessing fiber-related risks, at least when exposures are high. However, in this talc mine, exposure estimates derived from midget impinger measurements (Oestenstad et al., 2002), showed no such relationship. If cleavage fragments were responsible for the lung cancer excess, an exposure–response relationship would have been anticipated.

To date a satisfactory explanation for the observation of an overall excess of lung cancer and for the concentration of the excess in miners rather than millers has not been found for workers exposed to either NY or Vermont talc, although at least part of the excess among NY talc workers is due to smoking (Gamble, 1993; Honda et al., 2002). If the airborne dust contained over 70% amphibole asbestos fibers as reported by Dement et al. (1980), there should be an overall increased risk of lung cancer, which there is. But there should also be a logical increasing risk of lung cancer with increasing dust exposure, with a very high risk of lung cancer in highly exposed workers. This is clearly not the case.

In Finland where the incidence of cancer has been studied in anthophyllite miners, it was found that among heavily exposed male workers, the standardized incidence ratio (SIR) for lung cancer was 5.54 (CI = 3.90–7.63) and among moderately exposed workers it was 1.63 (0.20–5.89). The

heavily exposed were those who worked in the mine or mill and the moderately exposed included all other personnel (Meurman et al., 1994). This exposure–response pattern is quite the opposite of that in the New York talc mines and mills.

There were consistent positive exposure–response trends for lung cancer risk as occurred with the increased asbestiform amphibole exposure in the Libby cohort. The slope of the exposure–response curve was steeper for lung cancer than for pneumoconiosis and for mesothelioma (Fig. 4).

The clear exposure–response trends for lung cancer to increase with increasing exposure to asbestiform tremolite and anthophyllite is in marked contrast to the negative exposure–response trend for lung cancer risk to decrease with increasing exposure to non-asbestiform tremolite and anthophyllite present in industrial talc. The pattern of increasing risk of fibrosis is consistent with exposure to mineral dust with or without the presence of tremolite asbestos. These lung cancer comparisons are graphically displayed in Fig. 6.

## 19. Biological plausibility

Biological plausibility is not a necessary prerequisite to establishing a causal association, but it is considered “helpful” (Hill, 1965). Experimental evidence is available to consider whether or not cleavage fragments are more or less carcinogenic than asbestos fibers. These issues have been independently evaluated by Addison and McConnell and Mossman, elsewhere in this volume.

Experimental studies have the potential advantage of precisely defining the characteristics of the minerals and amount of exposure. However there are also difficulties that affect the studies and their interpretation. Hence it is important to examine the overall pattern of biological responses to asbestos fibers and cleavage fragments rather than the results of single studies. Feeding studies have been considered elsewhere (Wilson et al., 2008).

Many experiments in animals have been used to assess the potential of fibers to produce mesothelioma-type neoplasms. For example, Stanton et al. (1981) counted as a positive response, pleural sarcomas that resembled the mesenchymal mesothelioma of man. The observed response is a measure of potential hazard rather than risk. Nevertheless such studies have been helpful in suggesting the morphological characteristics of particles in relation to “mesothelioma” producing potency. “Index particles” have been derived from these experiments. For example, based on the work of Stanton and colleagues the index particle is  $>8\ \mu\text{m}$  long and  $<0.25\ \mu\text{m}$  wide and is the best predictor of tumors without regard to the chemical composition of the particle. As far as we were able to ascertain, few if any cleavage fragments have the combination of diameter less than  $0.25\ \mu\text{m}$  and length greater than  $8\ \mu\text{m}$ . This would suggest that cleavage fragments are not the most potent particles for the production of mesothelioma.

Different exposure techniques have been used, but most have not involved the inhalation route of exposure applicable to humans. Most experiments have involved placing fibers onto the pleural or into the peritoneal cavity or injections intratracheally, routes of exposure which are artificial. The incidence of tumors is therefore higher and the tests are likely to be more sensitive than by inhalation. However, these experiments ignore the factors which limit fiber passage to these sites and also the alterations to the particles during their passage to these sites if they get there at all. Nevertheless, these data are useful in hazard assessment, as the absence of “mesothelioma” occurrence when fibers are placed directly on the pleura or peritoneum in sufficient numbers, is strong evidence that human inhalation exposure is unlikely to be hazardous.

Samples used in experimental studies are not always related to the minerals to which workers are exposed. For example, no experimental studies of the Homestake gold ore were found. On the other hand, there are several studies of tremolitic talc samples from the Gouverneur mine in New York State (talc samples 6 and 7 used by Stanton et al. (1981); FD-14 used by Smith et al. (1979) and FD-275 (non-asbestiform tremolite) used by Smith et al. (1979) and by McConnell et al. (1983)) in feeding studies. Wylie et al. (1997) used *in-vitro* cell studies to compare the effects of asbestos fibers to talc fibers and transitional fibers in NY talc.

Fig. 7 shows the results of rat injection studies of asbestiform and non-asbestiform varieties of amphiboles, primarily tremolite. These data show a consistent pattern of high incidence of mesothelioma tumors with exposure to tremolite asbestos from South Korea, California, Swansea and Italy (Davis et al., 1985; Wagner and Berry, 1969; Wagner et al., 1982; Stanton et al., 1981). The mesothelioma incidence of both controls and samples was around 10%. The two Scottish tremolites studied contained relatively few asbestiform fibers and there was little difference between the control and exposed rats irrespective of whether the tremolite was asbestiform or not. Davis et al. (1991) noted that the intraperitoneal injection test used in their experiments is extremely sensitive so that any dust that produces fewer than 10% tumors is unlikely to show evidence of carcinogenicity by inhalation. Thus the non-asbestiform Scottish tremolite from Shinness was considered to pose no hazard.

The Scottish tremolite from Dornie was considered to be probably harmless as well. The latter sample was described as containing mostly cleavage fragments but also some very long, thin fibers, with a possible small asbestiform subpopulation. These results should be contrasted with those of asbestiform tremolite from Italy, California, Swansea and South Korea, which showed incidences of 70–100%. The Italian tremolite was described as a needle-like (byssolite) tremolite fiber but later shown to have an asbestiform component. For this fiber, the induction of tumors was much later than for the three asbestos types from California, Swansea and Korea. This is a normal response to a small

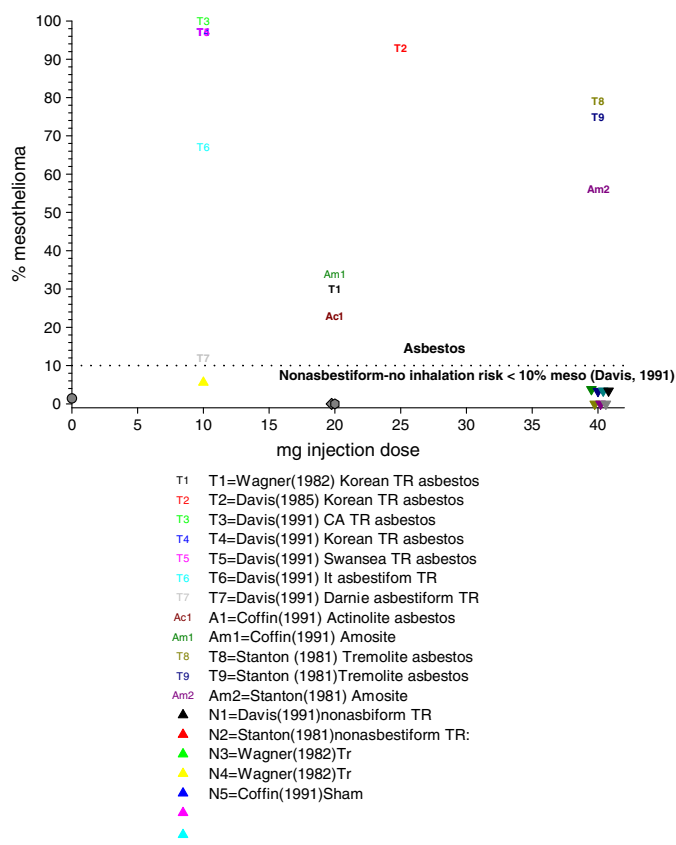


Fig. 7. Experimental studies of injections into rats of asbestiform amphiboles and non-asbestiform amphiboles.

dose of amphibole asbestos. Incidence was reduced to near zero for samples of non-asbestiform tremolite and talc fibers (Wagner et al., 1982; Stanton et al., 1981). Smith et al. (1979) assessed the incidence of tumors after injection of NY tremolitic talc and tremolite asbestos at two different doses. There were clear exposure–response trends for the asbestiform tremolite but no effect of non-asbestiform tremolite at either 10 or 25 mg exposures (Fig. 8).

## 20. Statistical analysis of potency by size, shape and mineralogy

Berman et al. (1995) conducted a statistical reanalysis of inhalation studies using data from studies of AF/HAN rats exposed to different types of asbestos to identify the exposure metrics that best predicted the incidence of lung cancer or mesothelioma. New exposure metrics were first generated from samples of the original dust because of limitations in the original characterizations. This analysis provided more detailed information on mineralogy [i.e., chrysotile, grunerite (amosite) asbestos, riebeckite (crocidolite), tremolite asbestos], type of structure (i.e., fiber, bundle, cluster, matrix), size (length, width) and complexity (i.e., number of identifiable components). In particular, transmission electron microscopy (TEM) was added to the descriptions so that asbestos structures less than

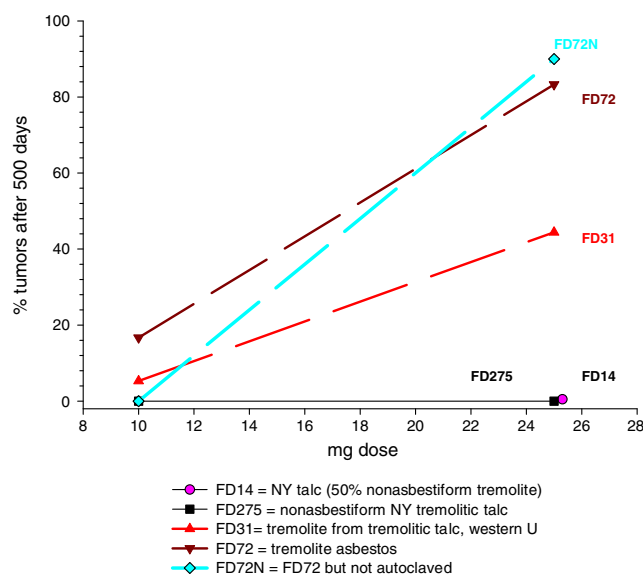


Fig. 8. Mesotheliomas in hamsters after intrapleural injection of tremolite asbestos and talc containing non-asbestiform tremolite Smith et al. (1979).

0.2  $\mu\text{m}$  could be detected and identified and used in the statistical analysis of size distributions to evaluate combined effects of length and width.

Implantation and injection studies generally indicate long, thin fibers are most likely to induce mesothelioma. However, Berman et al. (1995) considered inhalation studies more relevant for assessing human risk because lung retention and transport from the lungs are likely to be important variables in potency but are bypassed in the implantation/injection studies. Also the exposure metrics from these studies are unable to satisfactorily predict tumor incidence (for example see Oehlert, 1991).

The analysis by Berman et al. (1995) indicated that particles contributing to lung tumor risk are long ( $>5 \mu\text{m}$ ) thin ( $<0.4 \mu\text{m}$ ) fibers or bundles with the potency increasing as length increases. For example, thin fibers longer than 40  $\mu\text{m}$  are about 500 times more potent than thin fibers 5–40  $\mu\text{m}$  in length. Long and very thick particles ( $>5 \mu\text{m}$ ) may pose some risk, but these appear to be complex structures rather than fibers. It is hypothesized that these structures with large widths may break down and release additional long thin fibers or bundles. Short particles less than 5  $\mu\text{m}$  in length do not appear to pose any lung cancer risk in this database. Thus in rats a particle length of 5  $\mu\text{m}$  or less (or as Berman et al. suggest, 5–10  $\mu\text{m}$  or less) appears to have zero potency.

The only other available data set for quantitatively assessing particle size is that of Stanton et al. (1981). The Berman et al. (1995) data set is considered more relevant because

1. It is based on an inhalation rather than implantation route of exposure;
2. It includes a range of representative samples of both asbestos fiber-types and particle sizes;

3. There is a more detailed characterization of long particles and complex structures than any other experimental study; and
4. The statistical analysis is more appropriate.

The analysis by Berman et al. (1995) is more appropriate as logarithms were not used, which avoided the problem of zero exposures in some size ranges and 0 tumors at some exposures. Also, an optimum exposure index was determined that provides a statistically adequate fit to the data. The models used by Stanton et al. (1981) do not fit the data well and therefore do not adequately describe the ranking of particle size potency.

In a statistical reanalysis of the Stanton et al. (1981) data, Oehlert (1991) confirmed the Stanton hypothesis that the primary ability of mineral particles to cause tumors are their dimensional properties, namely index particles that are long and thin ( $>8\text{ }\mu\text{m}$  long and  $<0.25\text{ }\mu\text{m}$  wide). Using improved models that fit the data better, Oehlert (1991) reinforced the idea that very long, very thin particles were the best predictors for tumors and that particles with dimensions outside the index class did not contribute to carcinogenicity. This is also in agreement with Berman et al. (1995) that non-index particles have essentially zero potency.

Oehlert (1991) disagreed with the Stanton hypothesis that dimensions alone determine carcinogenic potency. Model fit was significantly improved by assessing each mineral type separately, which indicates mineral type is also important. This disagreement was unfounded, as in fact, Stanton, himself noted that the solubility of the fiber was also important, a parameter that would be incorporated in any analysis by considering fiber type. Dimensions are necessary but are not alone sufficient to classify a substance as capable of inducing tumors. It is now well established that factors such as particle solubility and perhaps surface properties are also important. For example, fibrous talc from the Gouverneur talc deposit in New York is not equivalent (0% tumor probability) to grunerite (amosite) asbestos (93% tumor probability) in tumor producing potential although the dimensions are similar (Stanton et al., 1981).

In sum, the Oehlert (1991) reanalysis of the Stanton et al. (1981) data is consistent with Berman et al. (1995) that particles of certain dimensions are important predictors of tumor incidence. Long and thin particles are the significant dimensions. Also, the minerals comprising sufficient particles in these size ranges to produce tumors included asbestos (crocidolite, amosite, and tremolite asbestos) but not the non-asbestiform amphibole mineral (tremolitic talc).

Given the importance of width and length from these experimental data, it is useful to summarize available data on dimensions of amphiboles in the epidemiological studies summarized in previous sections (Table 8).

This analysis indicates the low amounts or absence of long, thin particles in the size ranges that predict lung

tumors or mesothelioma in the three ore bodies containing non-asbestiform amphiboles (NY talc, taconite and Homestake). A primary interest in studying these workers is the fact that they were exposed to non-asbestiform amphiboles. Steenland and Brown (1995) expressed the interest as follows: “Non-asbestiform amphibole fibers have not been shown to cause lung cancer, *but are suspect because of their similarity to asbestiform fibers* (emphasis added)”. The data in Table 8 and noted above suggest that the similarity is applicable only to chemistry since there is no similarity in the occurrence of index particles. The long thin elongated particles (fibers) capable of inducing tumors are common in asbestiform amphiboles and absent in non-asbestiform amphiboles.

The absence of long thin particles in the size ranges identified by Stanton et al. (1981) and by Berman et al. (1995) as responsible for lung cancer and mesothelioma experimentally from ores containing non-asbestiform amphiboles detracts from the hypothesis that non-asbestiform particles have a carcinogenic potency similar to asbestos fibers. The other parameter which is now recognized as being important is biopersistence. As the cleavage fragments are in general shorter than the asbestos fibers they are likely to be more readily removed by macrophages than the asbestos. On the other hand, the solubility difference between cleavage fragments and fibers is not known, although Ilgren (2004) suggests greater solubility of cleavage fragments. However, it is possible that fibers, because they could split apart, would have greater surface areas and might be more soluble than cleavage fragments of the same dimensions. This would mean that they would have greater lung biopersistence than fibers. On this basis, long cleavage fragments would have the potential to pose a lung cancer/mesothelioma risk if cleavage fragments had the same biological potency as asbestos fibers of the same length.

In fact, this is not a real problem because the biopersistence of the amphibole fibers is known to be very high. Even if there were long cleavage fragments, their large diameters would reduce the risk compared to asbestos and their retention would be highly unlikely to render them more hazardous than the asbestos fibers. In this regard, it should be noted that the sample FD14 from the NY deposit did contain elongated particles that ranged up to  $50\text{ }\mu\text{m}$  in length (Griegner and McCrone, 1972) and did not produce mesothelioma.

Conclusions about cleavage fragments from some of the other experiments are somewhat limited because, for example, the sample of Greenland non-asbestiform tremolite studied by Wagner et al. (1982) had no fibers greater than  $10\text{ }\mu\text{m}$  in length and less than  $0.25\text{ }\mu\text{m}$  in width. The sample FD 275-1 did not contain any particles longer than  $10\text{ }\mu\text{m}$  in length and no particles with a width less than  $1\text{ }\mu\text{m}$ . Stanton (1973) showed that riebeckite (crocidolite) asbestos, pulverized to the state where 80% of the mass of fibres was in the size range less than  $10\text{ }\mu\text{m}$  in length, produced a “negligible incidence” of mesotheliomas in pleural implantation studies.

While it is reassuring that none of the samples of non-asbestiform tremolite have produced elevated rates of mesothelioma in experimental animals, it is unfortunate that systematic studies have not been done to determine whether cleavage fragments of the same lengths as asbestos fibers produce the same risks as doses have generally been measured on a mass basis and not on the basis of number of fibers or cleavage fragments of particular lengths. An obvious problem with cleavage fragment studies is that in order to achieve similar numbers of long thin fibers to the tremolite asbestos in the dose, there would have had to be a very much larger mass of cleavage fragments injected, and that alone would have produced difficulties in animal survival. There do not appear to be cleavage fragment-related increases in lung cancer or mesothelioma risk in the studies. The lack of risk may be related to the fact that workers in those industries are not exposed to high concentrations of long cleavage fragments and the fact that because of their diameters such fragments would carry a much lower carcinogenic potency than their equivalent asbestiform mineral.

Our review of the experimental literature did not reveal any findings which would indicate that cleavage fragments have the same or greater carcinogenic potential than asbestos. In fact, they indicated that amphibole cleavage fragments have a much lower carcinogenic potential than their asbestiform counterparts by many orders of magnitude. In conclusion, there are still many unanswered questions relating to the extent to which the asbestiform habit of a mineral influences its biological behavior relative to that of a cleavage fragment (size for size). But the experimental data do provide strong support for the epidemiological findings that the risks of lung cancer and mesothelioma are considerably less [or absent] for persons exposed to amphibole cleavage fragments when compared to persons exposed to amphibole asbestos fibers.

## 21. Other amphiboles and other minerals

A search of the literature for studies containing both health outcomes and descriptions of exposure to cleavage fragments failed to identify additional studies that would be of immediate assistance in examining the health risks associated with cleavage fragments. The review did identify studies such as that in Finland where the percentages of asbestiform tremolite and cleavage fragments and fibrous wollastonite and cleavage fragments of wollastonite were characterised in metamorphic limestone and dolomite mines (Junttila et al., 1996). However, epidemiological studies to relate to the environmental studies do not appear to be available. The exposure to “Federal fibers” in quarrying industries and coal mines with their large workforces would be of interest. There were experimental studies and health evaluations of arfvedsonite asbestos in Russia (Kogan et al., 1970; Pylev and Iankova, 1975). There were well described studies of crocidolite-exposed populations,

but no health studies of workers exposed to non-asbestiform riebeckite have been identified.

There are potentially other populations of workers exposed to the hundreds of other minerals (e.g., erionite; fluoroedenite), which can occur with a fibrous morphology. There is some information on mesothelioma risks for some of these minerals, but no studies were found of populations exposed to the non-asbestiform fibers of these same minerals.

A chronic intraperitoneal injection study administered doses of asbestiform silicon carbide (SiC) whiskers and SiC cleavage fragments to rats. The purpose of the study was to compare potency by particle size. Cleavage fragments were defined as longer than 5 µm, narrower than 3 µm and aspect ratios greater than 3:1. Only 3.3% of cleavage fragments had aspect ratios greater than 10:1 compared to 96% for whiskers; lengths greater than 10 µm were 0% for cleavage fragments and 44% and 30% for low and high doses of asbestiform whiskers. Tumor rates for cleavage fragments were 0.8% and 0% for low and high doses respectively; 20% and 43% tumors rates were expected if cleavage fragments had the same potency as asbestiform whiskers (Rodelsperger and Bruckel, 2006). These data are consistent with the amphibole experimental data showing that cleavage fragments (or even federal fibers) “have a much lower carcinogenic potency than whiskers, if any at all.”

While the gaps in knowledge concerning the US studies need to be filled, a broader base of information would be helpful. In the absence of well defined occupational groups exposed to well-characterised cleavage fragments with well studied health outcomes, it may be useful to consider non-occupational settings. In some of these areas, there are definite concentrations of pleural calcification and definite areas of elevated rates of malignant mesothelioma. Perhaps mapping the geographical distribution of mesothelioma in various countries such as Southern Europe, New Caledonia and the Mediterranean region might identify clusters of cases which might be investigated for asbestiform amphibole exposure and non-asbestiform amphibole exposure in for example, case-comparison studies.

## Conflict of Interest

The authors declare that they have no conflicts of interest.

## Funding Source

The article funded by The National Stone and Gravel Association.

## Acknowledgments

We acknowledge with thanks the very helpful comments of Dr. Anne G. Wylie, Mr. John Addison, Dr. EE McCon-

nell, and Mr. J. Kelse. This work would not have been possible without financial support from the National Stone Sand and Gravel Association, Alexandria, Virginia.

## Appendix A

There is some overlap between this appendix and the main text in order to maintain the historical development of knowledge concerning the NY talc deposit.

### A.1. New York State talc

#### A.1.1. Early NY talc studies

Kleinfeld et al. (1967) conducted a PMR mortality study among 220 talc miners/millers with 15 or more years of exposure in 1940, with follow-up to 1965. There were 28 deaths (31%) attributed to pneumoconiosis and complications and a PMR of 3.44 for 9 deaths from lung cancer and 1 from fibrosarcoma of the pleura. Kleinfeld et al. (1967) also reported that in a small group of asbestos insulation workers with similar years of exposure, the asbestos workers had about twice the proportion of lung cancer deaths (24% vs 11%) and the significant excess was in both the 40–59 and 60–79 year age groups. This is “at variance” with the talc workers where the excess was only in the 60–79 year age group (PMR = 4.36) and a deficit (PMR = 0.96) in the 40–59 year age group. Overall, lung cancer mortality among the asbestos insulators was 2.5 times higher than among the talc workers, 8.43 versus 3.44.

Kleinfeld et al. (1974) added 4 more years of follow-up (to 1969), 40 more workers in the cohort (for a total of 260), 17 more total deaths (for a total of 108) and three more respiratory cancers (for a total of 13). Similar results to the 1967 study were obtained with the only significant excess of respiratory cancers in the 60–79 age range (PMR = 4.61) and not in the 40–59 year age group (PMR = 1.63). The authors thought it was noteworthy that the significant excess respiratory cancer mortality was in the years 1945–1959 (PMR = 3.37) and not in the years 1960–1969 (PMR = 1.35) when dust counts were appreciably reduced but fiber counts (fibers/mL >5 µm) remained high. Ten of the 13 respiratory cancer deaths occurred in workers exposed 15–24 years (and about the same latency). The authors suggested a more susceptible group develops cancer between 15 and 24 years leaving a less susceptible group in spite of more years of exposure. The size of the cohort is too small to confirm this hypothesis. There was one case of peritoneal mesothelioma but no information regarding latency or other work exposures.

Exposure was characterized as predominantly talc admixed with silicates such as serpentine, tremolite, carbonates and a small amount of free silica. Exposures were quite high before 1945 when both pneumoconiosis and lung cancer cases began working. Wet drilling began after 1945, which reduced mine levels from 818 to 5 mppcf. Exposures were lower in the mill than the mine prior to

1945, but after 1945 were not reduced as much as in the mine and were now 5 times (or more) higher than in the mine. Workers with lung disease had initial exposures prior to 1945 before wet drilling began and when average dust counts in the mine were 818 (83–2800) mppcf for drilling and 120 (2–475) for mucking. In the mill, averages were 180, 69, 92 and 151 mppcf for crushing, screening, milling and bagging. After 1945 (1946–1965) average dust counts were reduced to about 5 mppcf in these jobs in the mine and in the mill averages were generally below 50 mppcf.

Kleinfeld et al. (1973) studied 39 workers exposed to commercial talc dust where tremolite and anthophyllite were the major fibrous components. They also examined 16 talc samples from different mining and milling operations as well as finished products from NY State. Analyses included polarized LM, TEM with selected area diffraction, X-ray diffraction and electron microprobe analysis. No data are provided on distribution by fiber sizes. The point is made that there was no correlation between fiber count (fibers >5 µm) and mean dust counts (mppcf). Particles observed included “true talc, talc fibers, serpentine minerals and after fragments, and amphibole fibers and fragments”. Fiber counts “may not provide a true picture of exposure to asbestiform minerals because the fiber counts include talc fibers but exclude many small asbestos fibers and ‘aggregate fibers’ which may contain substantial amounts of asbestiform minerals”. The electron micrographs of amphibole fibers present in talc suggested amphibole cleavage fragments.

*A.1.1.1. NY Tremolitic talc.* Brown et al. (1980) reported the dimensions of fibers determined by electron microscopy. Only 3% of tremolite fibers and 8–10% of anthophyllite fibers were longer than 5 µm; median lengths were about 1.5 µm. Median aspect ratios of 7.5 and 9.5 were reported for all fiber lengths of tremolite and anthophyllite. Data were not provided on aspect ratios for fibers >5 µm counted using phase contrast microscopy.

There then began a series of mortality studies of workers at the Gouveneur talc mine and mill in NY state (GTC) (Brown et al., 1979, 1980, Brown et al., 1990; Stille and Tabershaw, 1982; Lamm et al., 1988; Gamble, 1993; Honda et al., 2002; Oestensstad et al., 2002). The extensive literature on GTC talc centers on three major issues that started with the first NIOSH mortality and industrial hygiene study of GTC workers.

*Is the reported excess SMR for lung cancer due to the alleged asbestiform amphiboles in the talc or due to confounding? Confounding factors could include other work exposure (primarily in the surrounding mines/mills), from life-style factors such as smoking or short-term employees.*

*Is the tremolite and anthophyllite content of the talc non-asbestiform cleavage fragments or is the talc contaminated with tremolite asbestos and anthophyllite asbestos?*

*Is there biological plausibility that the tremolitic talc acts like asbestos producing asbestos-like effects in animal studies?*

### A.2. Epidemiology of health effects of GTC talc

Brown et al. (1979, 1980) studied 398 white males first employed 1947–1959 with vital status determined as of 1975. There was a 2.73-fold excess risk of lung cancer. Risk increased with increasing latency with SMRs of 2.00 and 4.62 at 10–19 and 20–28 years latency, which was said to be “consistent with an occupational etiology”. There was no analysis by years worked although 4/9 cases had worked less than 1 year. Smoking was considered unlikely to account for all the increased risk by Brown et al. (1979, 1980). Exposures in surrounding mines and mills were higher but all were said to involve exposures to “asbestiform amphiboles”. Exposures to “asbestiform tremolite and anthophyllite stand out as the prime etiologic factors associated with the observed increase in bronchogenic cancer”.

Stille and Tabershaw (1982) studied 655 white males employed 1948–1977 with vital status determined at the end of 1978. Lung cancer was only significantly elevated among employees with any prior employment history. There was no analysis by years worked and latency was not taken into account.

Because of these conflicting findings, Lamm et al. (1988) reanalyzed these data. They studied 725 male talc workers who had ever worked at Vanderbilt since the plant opened in 1947 through the end of 1977 with follow-up through 1978. Previous employment obtained from job applications were classified as posing a prior risk, no prior risk or unclassifiable (no indication of prior work history) with regard to risk of lung cancer. Among those with more than 1-year employment the SMRs for lung cancer and non-infectious, non-neoplastic respiratory diseases were 1.93 and 3.70, respectively, compared to 3.00 and 0 for those with less than 1-year duration. Adding prior exposure history to the analysis showed that lung cancer risk appeared to be related to prior employment. The SMRs were similar for all job risk categories, although the number of cases was too small to be definitive. Mean latency was 20.8 years (12–25) and all those with less than 20 years latency since being hired at GTC had worked elsewhere. Five of the 12 cases had 3 months or less employment. The authors conclude the increased risk of lung cancer in this cohort of talc workers is concentrated in short-term workers, probably due to prior employment, smoking or other differences in behavioral characteristics.

At the request of RT Vanderbilt and Company, NIOSH conducted a health hazard evaluation (HHE) of the GTC cohort (Brown et al., 1990). Eight years of follow-up (through 1983) and an analysis by latency and tenure were added to the retrospective cohort study. Nearly a third (27%) of the cohort had died, with 161 total deaths and 17 lung cancer deaths with an overall SMR of 2.07. About 50% of the cohort had worked less than 1 year. Among the 13 lung cancer cases with 20 or more years latency, there was a 3.6-fold excess in the eight cases with less than a year tenure Vs. a nonsignificant SMR of 1.79 among the five

cases with >1-year tenure. There were also 17 NMRD deaths with an overall SMR of 2.50 (1.46–4.01). Six of the cases had worked for less than 1 year with an SMR of 1.94 (0.72–4.28). There was a 3-fold excess (SMR 2.89; 1.45–5.18) among those with more than 1-year tenure. This pattern for NMRD is “more consistently associated with an occupational exposure at GTC”. Principal limitations in this study were small size (especially those with long tenure), inability to precisely characterize past occupational exposures at GTC or elsewhere, and lack of reliable smoking history. The authors concluded it is unlikely these potential confounders alone could account for the observed excess risks.

Gamble (1993) conducted a case control nested in the Brown et al. (1990) cohort. Information was collected on smoking, time exposed to talc plus a risk ranking on non-talc exposure. There were 22 cases and 66 controls matched on date of birth and date of hire. There were zero non-smokers among the cases (91% smokers and 9% ex-smokers) compared to 27% non-smokers, 73% smokers or ex-smokers among controls. Inverse trends were consistently observed by years worked for different subsets of the study population; e.g., all cases and controls, smokers only, those with >20-years latency, total tremolitic talc years. The author concluded that “after adjustment for...smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure”. The time occurrence of lung cancer was consistent with a smoking etiology, and was not consistent with an occupational relationship.

Finally, Honda et al. (2002) assessed cancer and non-cancer mortality among white male GTC talc workers. The cohort analyzed for cancer mortality consisted of 809 workers employed 1947–1989 and alive in 1950. The cohort analyzed for non-cancer mortality consisted of 782 men employed during 1960–1989. The important additions in this study were 6 more years of follow-up (through 1989) and internal exposure–response analyses with cumulative exposure to talc dust as the exposure variable. Overall mortality continued to remain elevated at 1.31 ((209/160) due largely to 2.32-fold excess from lung cancer (31/13) and 2.21-fold excess in NMRD (28/13). The patterns are consistent with previous results, in particular with the inverse lung cancer trends from the nested case–control study (Gamble, 1993) and the inverse relationships for NMRD and lung cancer reported by Lamm et al. (1988). Honda et al. (2002) reported that among workers with >20-years latency, there was a 3.3-fold excess lung cancer for <5-years tenure and 1. Ninefold excess for >5-years tenure. For other NMRD (COPD + pneumoconiosis and excluding pneumonia, influenza, asthma, emphysema and bronchitis) the SMRs were 2.71 and 3.02, respectively. The internal comparisons by cumulative exposure (mg/m<sup>3</sup> years) and adjusted for age and latency, showed a significant monotonic decrease in lung cancer risk with increasing exposure with a RR of 0.5 (0.2–1.3) in the highest exposure category. Mortality from ‘other NMRD’ and

Table A1

Exposure differences between cases of lung cancer, Other NMRD and Fibrosis in NY talc workers (Honda et al., 2002)

	Lung cancer	Other NMRD	Fibrosis
Median years worked	1.0	8.3	11.8
Median cumulative exposure (mg/m <sup>3</sup> days)	347	1199	3759

pulmonary fibrosis showed monotonic increases in risk as exposure increase. Risks were increased 2- and 12-fold increased risks in the highest exposure categories (Fig. 3).

There were two cases of mesothelioma, but because of too short latency in one case and minimal exposure for a

short time, Honda et al. (2002) considered it unlikely that exposure to talc ore was the cause.

Because of too short latency, Honda et al. (2002) concluded that the cause of the increased lung cancer mortality in the cohort is unclear, but speculated that it could be due in part to smoking or “other unidentified risk factors”. They suggest it is unlikely to be related to talc ore dust per se. Other NMRD (and in particular fibrosis) were considered causally related to talc ore dust, other dusts in other work environments and smoking. This conclusion is supported by the differences in years worked and median cumulative exposures among decedents with these three causes of death and the inverse E-R trend for lung cancer (Table A1).

Table A2

Summary of results for lung cancer and mesothelioma from studies of NY talc workers

Reference	Study characteristics	Lung cancer	Mesothelioma
Kleinfeld et al. (1967)	220 NY Talc Miners $\geq 15$ years tenure in 1940; 1965 follow-up, 91 total deaths, PMR	PMR = 3.44 (1.65–6.3) (11 deaths)	1 peritoneal mesothelioma (1.1%)
Kleinfeld et al. (1974)	260 NY Talc Workers $\geq 15$ years in 1940 or between 1940 and 1969; 108 total deaths, PMR, follow-up of Kleinfeld et al. (1967)	PMR resp cancer = 3.24 (1.72–5.54) (12 lung cancer, 1 fibrosarcoma of pleura)	1 peritoneal mesothelioma (0.93%)
Brown et al. (1979, 1980)	398 WM employed GTC 1947–1959, follow-up 1975; 18% <1 month, 24% 1–6 months, 50% <1 year; 44% <1950;	9/3.3 = 2.73 (1.25–5.18) ( $p < 0.05$ ); 4 <1-year tenure	1/74 = 1.4% (16-year talc tenure, 11 years construction)
Stille and Tabershaw (1982)	655 WM employed GTC 1948–1978, vital status 1978;	10/6.4 = 1.57 (10 obs)  Prior employment = 2.14 (8 obs) No prior work = 0.76 (2 obs)	
Lamm et al. (1988)	705 men employed GTC 1947–end 1977, vital status 1978	12/5 = 2.40 (1.24–4.19)  >1 year 6/3.1 = 1.93 (0.71–4.20) prior risk = 3.08 (6/2) <1 year 6/1.9 = 3.16 (0.16–6.88) prior risk = 3.33 (3/0.9)	1 electrician 15-year latency; 20-years prior  As miner, miller, construction
Brown et al. (1990)	710 WM employed at GTC 1947–1978 with vital status 1983; Not reported,	17/8.2 = 2.07 (1.20–3.31)  <1-year = 3.64 (1.54–7.04) 1–9 years = 0.83 (0.02–4.57) 10–19 years = 4.0 (0.54–16.1) 20–36 years = 1.82 (0.21–6.36)	
Gamble (1993)	22 lung cancer cases at GTC 1947–1978 matched 3:1 on data of birth and date of hire.	OR lung cancer  Tenure smokers >20-year latency <5 year 1.0 5–15 years 0.63 15–36 years 0.42 mg/m <sup>3</sup> days RR ( $n$ )  <95 1.0 (11) <987 0.8 (9)  987 + 0.5 (9) Hired: <1955 SMR 2.86 (0.9–4.1) Hired > 1955 SMR: 0. (0.2–2.4)	
Honda et al. (2002)	809 WM talc workers employed GTC 1948–1989 follow-up  Cancer: 1950–1989 Non-cancer mortality = 1960–1989		Two cases not considered causal due to short latency,  Case 1 & Very low exposure, Case 2 (3.7%)

All but two of the studies (Kleinfeld et al., 1967, 1974) were the same cohort of GTC workers.

Pn, pneumoconiosis.

These results are not at all consistent with the dust causing fibrosis being responsible for the lung cancer excess.

### A.3. Summary of results from studies of NY talc workers

The cohorts studied before 1979 by Kleinfeld and colleagues worked in talc mines in St. Lawrence County, NY. After 1978 the cohorts were comprised of workers at the Gouverneur mine and mill, some of whom had previous employment in other mines in St. Lawrence County, NY (Table A2).

The authors of the two NIOSH studies of GTC talc (Brown et al., 1979, 1980; Brown et al., 1990) concluded that the tremolite and anthophyllite were the most likely etiological agents. This conclusion is based on the following logic.

*The excess risk of lung cancer and NMRD were consistent with the findings of Kleinfeld et al. (1967, 1973) among NY talc workers and Meurman et al. (1974, 1979) among anthophyllite asbestos miners. The etiological agents were considered to be “asbestiform tremolite and anthophyllite,” which were said to be in both talc ores at concentrations well above standards. Smoking could not account for the excess lung cancer risk. Short-term workers may have had “very high exposures, especially in the early years of the mining operation,” which might account for their excess risk (Brown et al., 1990). There was an increased risk of developing pleural changes (including pleural thickening and pleural calcification), and the prevalence is higher when there is exposure to anthophyllite (Dement et al., 1980).*

*The lack of an association with years worked could be due to a combination of factors above plus work in other talc operations and/or other work-related exposure to lung carcinogens.*

Many of these arguments have been contradicted by further analyses.

Kleinfeld et al. (1967) compared lung cancer risk patterns of talc workers with (apparently) their own data for a similar group of asbestos insulation workers. The asbestos PMRs were 2–3 times higher among the asbestos workers for lung cancer and GI cancers. Kleinfeld et al. commented that a major difference was the increased risk of lung cancer in age groups of 40–59 and 60–79 among asbestos workers, but excesses for talc workers were among only the 60–79 age group. In addition, longevity of talc miners was longer than the national average. Age at death among the talc lung cancer cases was 3 years greater than the average of all deaths and 10 years greater than the U.S. average. The talc lung cancer cases occurred in persons exposed before wet drilling was introduced. Wet drilling reduced mean exposures 164-fold from an average of 818 mppcf to 5. Kleinfeld et al. (1967) suggested part of the reason for the earlier deaths of asbestos cases compared to talc cases “may be partly due to the greater carcinogenicity of asbestos dust or to an increased level of exposure to asbestos or both”.

There was excess mortality among the NY talc workers, but considerably less than the risk of asbestos workers

exposed in the same time period. It is not possible to directly compare risks from the Kleinfeld et al. (1974) cohort with that of the GTC cohort. The Kleinfeld et al. cohort et al is older, had worked decades earlier than the GTC cohort, and consisted of workers with more than 15 years tenure. Vanderbilt workers included many short-term workers with 26 years as the maximum possible years worked and no analysis by years-worked (Brown et al., 1979, 1980). In addition, overall mortality was over twice as great in the Kleinfeld et al cohort, i.e., 42% vs. 19%. *When stratified by years worked in subsequent follow-ups there were two cases with >20 years tenure (SMR = 1.82) and five cases with >10-years tenure (SMR = 2.17) (Brown et al., 1990). Gamble (1993) reported risk ratios less than 1.0 for lung cancer cases with >15-years tenure and adjusted for smoking. These data are suggestive of a different mortality pattern of GTC talc workers compared to the Kleinfeld talc cohort.*

*Smoking. Further updates of the GTC cohort revealed that all of the lung cancer cases were either smokers or former smokers, while only 73% of controls had ever smoked. Smoking latencies for GTC cases were consistent with latencies from studies of smokers. This is particularly true for short-term workers where the risk of lung cancer was highest and talc exposure too short to be plausible. Lung cancer risk among workers with more than 1-year exposure was increased about 2-fold compared to the US population. This degree of increased risk is in large part plausibly attributable to smoking (Gamble, 1993).*

*High exposure of short-term workers. Gamble (1993) matched on date of hire in the nested case control study of lung cancer. Thus, cases and controls had equivalent opportunities for very high exposures. Six of the lung cancer cases had less than 3-months tenure, several with only a few days, so there were very few opportunities for excessive cumulative exposure. Honda et al. (2002) showed that lung cancer cases had lower exposures than other subgroups. For example, median cumulative exposure of lung cancer decedents was 347 mg/m<sup>3</sup> days, which was less than all decedents (520), ischaemic heart disease decedents (376), all NMRD decedents (888), other NMRD decedents, pulmonary fibrosis decedents (3759). Thus there is no evidence to support the speculation that excessively high exposure in short-term workers could explain their increased risk.*

*Pleural changes. Gamble et al. (1979a,b, 1982) showed that the prevalence of pleural changes in GTC talc workers was essentially the same among other workers exposed to talc containing no measurable quantities of amphiboles. Thus it would appear that the pleural thickening observed in NY talc workers and other talc workers is likely due to factors other than exposure to amphiboles.*

*Exposure–response (E–R). The inverse exposure–response trends with duration of exposure were present when adjustments were made for other talc exposures and potential exposure to other work-related carcinogens (Gamble, 1993). The inverse E–R trends for lung cancer and cumulative exposure are strong arguments against attributing increased risk*

*of lung cancer to talc exposure. This argument is further strengthened by the very strong exposure–response relationship between fibrosis and cumulative talc exposure as well as the higher exposure of NMRD and fibrosis cases compared to lung cancer cases (Honda et al., 2002).*

## References

- Acheson, E.D., Gardner, M.J., Winter, P.D., Bennett, C., 1984. Cancer in a factory using amosite asbestos. *Int. J. Epidemiol.* 13, 3–10.
- Addison, J., McConnell, E.E., 2008. A review of carcinogenicity studies of asbestos and non-asbestos tremolite and other amphiboles. *Regul. Toxicol. Pharm.* 52, S187–S199.
- Addison, J., 2004. Personal communication 6, 2004.
- Allison, A.C., 1973. Experimental methods of cell and tissue culture: effects of asbestos particles on macrophages, mesothelial cells and fibroblasts. In: Bogovski, P., Gilson, J.C., Timbrell, V., & Wagner, J.C. (Eds.), *Biological Effects of Asbestos. Proceedings of a Working Conference*. Lyons, 2–6 October, 1972. Lyons, International Agency for Research on Cancer, pp. 89–93.
- Amandus, H.E., Wheeler, R., Jankovic, J., Tucker, J., 1987a. The morbidity and mortality of Vermiculite Miners and Millers exposed to tremolite–actinolite: Part I. Exposure estimates. *Am. J. Ind. Med.* 11, 1–14.
- Amandus, H.E., Wheeler, R., 1987b. The morbidity and mortality of vermiculite miners and millers exposed to asbestiform tremolite–actinolite. Part II. Mortality. *Am. J. Ind. Med.* 11, 15–26.
- Amandus, H.E., Althouse, R., Morgan, W.K.C., Sargent, E.N., Jones, R., 1987c. The morbidity and mortality of vermiculite miners and millers exposed to asbestiform tremolite–actinolite. Part III. Radiographic findings. *Am. J. Ind. Med.* 11, 27–37.
- Atkinson, G.R., Rose, D., Thomas, K., Jones, D., Chatfield, E.J., Goings, J.E., 1982. Collection, analysis and characterization of vermiculite samples for fiber content and asbestos contamination. MRI report for the Environmental Protection Agency, Project 4901-A32 under EPA contract 68-01-5915.
- Berman, D.W., Crump, K.S., Chatfield, E.F., Davis, J.M.G., Jones, A.D., 1995. The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF rats following inhalation. *Risk Anal.* 15, 181–195.
- Bernstein, D.M., Mast, R., Anderson, R., Hesterberg, T.W., Musselman, R., Kamstrup, O., Hadley, J., 1994. An experimental approach to the evaluation of the biopersistence of respirable synthetic fibers and minerals. *Environ. Health Persp.* 102 (5), 15–18.
- Berry, G., 1999. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. *Inhal. Toxicol.* 11, 111–130.
- Boundy, M.G., Gold, K., Martin Jr., K.P., Burgess, W.A., Dement, J.M., 1979. Occupational exposures to non-asbestiform talc in Vermont. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Inc, Park Forest South, Illinois, pp. 365–378.
- Brown, D.P., Sanderson, W., Fine, L.J., 1990. Health hazard evaluation Report HETA No. 90-390-2065 and MHETA 86-012-2065. RT Vanderbilt Company, Gouverneur, NY.
- Dement, J.M., Zumwalde, R.D., Gamble, J.F., Fellner, W., DeMeo, M.J., Brown, D.P., Wagoner, J.P., 1980. Occupational exposure to talc containing asbestos, morbidity, mortality, and environmental studies of miners and millers I. environmental study, II. Cross Sectional Morbidity Study, III. Retrospective Cohort Study of Mortality, NIOSH Technical Report, DHEW (NIOSH) Publication No. 80-115.
- Brown, D.P., Dement, J.M., Wagoner, J.K., 1979. Mortality patterns among miners and millers occupationally exposed to asbestiform talc. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Park Forest South, Illinois, pp. 317–324.
- Brown, D.P., Kaplan, S.D., Zumwalde, R.D., Kaplowitz, M., Archer, V.E., 1986. Retrospective cohort mortality study of underground gold mine workers. In: Goldsmith, D., Winn, D., Shy, C. (Eds.), *Silica, Silicosis, and Lung Cancer*. Praeger, New York, pp. 335–349.
- Campbell, W.J., Steel, E.B., Virta, R.L., Eisner, M.H., 1979. Characterization of cleavage fragments and asbestiform amphibole particulates. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publishers, Park Forest South, Illinois, pp. 276–285.
- Clark, T.C., Harrington, V.A., Asta, J., Morgan, W.K.C., Sargent, E.N., 1980. Respiratory effects of exposure to dust in taconite mining and processing. *Am. Rev. Respir. Dis.* 121, 959–966.
- Coffin, D.L., Palekar, L.D., Cook, P.M., 1982. Tumorigenesis by a ferroactinolite mineral. *Toxicol. Lett.* 13, 143–149.
- Coggiola, M., Bosio, D., Pira, E., Piolatto, P.G., Vecchia, C.L., Negri, E., Michelazzi, M., Bacaloni, A., 2003. An update of a mortality study of talc miners and millers in Italy. *Am. J. Ind. Med.* 44, 63–69.
- Cook, P.M., Glass, G.E., Tucker, J.H., 1974. Asbestiform amphibole minerals: detection and measurement of high concentrations in municipal water supplies. *Science* 185, 853–855.
- Cooper, W.C., Wong, O., Trent, L.S., Harris, F., 1992. An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J. Occup. Med.* 34, 1173–1180.
- Cooper, W.C., Wong, O., Graebner, R., 1988. Mortality of workers in two Minnesota taconite mining and milling operations. *J. Occup. Med.* 30, 506–511.
- Crane, D.T., 1986. Memorandum from OSHA Salt Lake City Analytical Laboratory—Microscopy Branch to Greg Piacitelli, NIOSH, Morgantown, West Virginia (November 26, 1986).
- Davis, J.M.G., Addison, J., McIntosh, C., Miller, M., Niven, K., 1991. Variations in the carcinogenicity of tremolite dust samples of differing morphology. *Ann. N. Y. Acad. Sci.* 643, 473–490.
- Davis, J.M.G., Addison, J., Bolton, R.E., Donaldson, K., Jones, A.D., Miller, B.G., 1985. Inhalation studies on the effects of tremolite and brucite dust in rats. *Carcinogenesis* 6, 667–674.
- Dement, J.M., Zumwalde, R.D., Wallingford, K.M., 1976. Discussion paper: asbestos fiber exposures in a Hard Rock Gold Mine. *Ann. N. Y. Acad. Sci.* 271, 345–352.
- Dement, J.M., Zumwalde, R.D., Gamble, J.F., Fellner, W.F., DeMeo, M.J., Brown, D.P., Wagoner, J.K., 1980. Occupational exposure to talc containing asbestos I. Environmental Study, DHEW (NIOSH) Publication No. 80-115, US DHEW/PHS/CDC/NIOSH, February, 1980.
- Dunn Geoscience Corp., 1985. An evaluation of mineral particles at Gouverneur Talc Company 1975 and 1982: a comparison of mineralogical results between NIOSH and DGC, Contract analysis and report to the R.T. Vanderbilt Company, Inc (January 4, 1985).
- Enterline, P.E., Henderson, V.L., 1987. Geographic patterns for pleural mesothelioma deaths in the United States, 1968–81. *J. Natl. Cancer Inst.* 79, 31–37.
- Fitzgerald, E.F., Stark, A.C., Vianna, N., Hwang, S.A., 1991. Exposure to asbestiform minerals and radiographic chest abnormalities in a talc mining region of upstate New York. *Arch. Environ. Health* 46, 151–154.
- Gamble, J.F., 1993. A nested case control study of lung cancer among New York talc workers. *Int. Arch. Occup. Environ. Health* 64, 449–456.
- Gamble, J.F., Greife, A., Hancock, J., 1982. An epidemiologic-industrial hygiene study of talc workers. *Ann. Occup. Hyg.* 26, 841–859.
- Gamble, J.F., Fellner, W., DeMeo, M.J., 1979a. An epidemiologic study of a group of talc workers. *Am. Rev. Respir. Dis.* 119, 741–753.
- Gamble, J., Fellner, W., DiMeo, M.J., 1979b. Respiratory morbidity among miners and millers of asbestiform talc. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Park Forest South, Illinois, pp. 307–316.
- Gibbs, A.R., Gardner, M.J., Pooley, F.D., Griffiths, D.M., Blight, B., Wagner, J.C., 1994. Fiber levels and disease in workers from a factory predominantly using Amosite. *Environ. Health Perspect.* 102 (5), 261–263.
- Gibbs, G.W., Hwang, C.Y., 1980. Dimensions of Airborne Asbestos Fibers, In: Wagner, J.C. (Ed.), *Biological effects of mineral fibres*.

- Proceedings of a Symposium held at Lyons, 25–27 September, 1979. Lyons, International Agency for Research on Cancer, IARC Scientific Publications No. 30, vol. 1, pp. 69–78.
- Gilliam, J.D., Dement, J.M., Lemen, R.A., Wagoner, J.K., Archer, V.E., Blejer, H.P., 1976. Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. *Ann. N. Y. Acad. Sci.* 271, 336–344.
- Griegner, G., McCrone, W.C., 1972. McCrone associates analysis of tremolitic talc FD-14 5.
- Harvey, A.M., 1979. Tremolite I Talc-a Clarification in Industrial Minerals. Metal Bulletin Limited, Worchester Park Survey, England, pp. 23–59.
- Higgins, I.T., Glassman, J.H., Oh, M.S., Cornell, R.G., 1983. Mortality of reserve mining company employees in relation to taconite dust exposure. *Am. J. Epidemiol.* 118, 710–719.
- Hill, A.B., 1965. The environment and disease: association or causation? *Proc. Roy. Soc. Med.* 58, 295–300.
- Hodgson, J.T., Darnton, A., 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann. Occup. Hyg.* 44, 565–601.
- Honda, Y., Beall, C., Delzell, E., Oestenstad, K., Brill, I., Matthews, R., 2002. Mortality among workers at a talc mining and milling facility. *Ann. Occup. Hyg.* 46 (1), 575–585.
- Hull, M.J., Abraham, J.L., Case, B.W., 2002. Mesothelioma among workers in asbestiform fiber-bearing talc mines in New York State. *Ann. Occup. Hyg.* 46 (1), 132–135.
- Ilgren, E.B., 2004. The biology of cleavage fragments: a brief synthesis and analysis of current knowledge. *Indoor Built Environ.* 13, 343–356.
- Junttila, S., Tossavainen, A., Hartikainen, T., Harma, P., Korhonen, K., Suominen, V., Pyy, L., 1996. Airborne mineral fibers and quartz dust in Precambrian metamorphic limestone and dolomite mines in Finland. *Appl. Occup. Environ. Hyg.* 11, 1075–1080.
- Karjalainen, A., Meurman, L.O., Pukkala, E., 1994. Four cases of mesothelioma among Finnish anthophyllite miners. *Occup. Environ. Med.* 51, 212–215.
- Kelse, J.W., Thompson, C.S., 1989. The regulatory and mineralogical definitions of asbestos and their impact on amphibole dust analysis. *Am. Ind. Hyg. Assoc. J.* 50, 613–622.
- Kleinfeld, M., Messite, J., Langer, A.M., 1973. A study of workers exposed to asbestiform minerals in commercial talc manufacture. *Environ. Res.* 6, 132–143.
- Kleinfeld, M., Messite, J., Zaki, M.H., 1974. Mortality experiences among talc workers: a follow-up study. *J. Occup. Med.* 16, 345–349.
- Kleinfeld, M., Messite, J., Kooyman, O., Zaki, M., 1967. Mortality among talc miners and millers in New York State. *Arch. Environ. Hlth.* 14, 663–667.
- Kogan, F.M., Valagov, A.G., Bunimovich, G.I., 1970. Health evaluation of the production of magnesite-arfvedsonite. *Gig. Tr. Prof. Zabol.* 14 (10), 45–47 (in Russian).
- Lamm, S.H., Levine, M.S., Starr, J.A., Tirey, S.L., 1988. Analysis of excess lung cancer risk in short-term employees. *Am. J. Epidemiol.* 127, 1202–1209.
- Langer, A.M., Maggiore, C.M., Nicholson, W.J., Rohl, A.N., Rubin, I.B., Selikoff, I.J., 1979. The contamination of Lake Superior with amphibole gangue minerals. *Ann. N. Y. Acad. Sci.* 330, 549–572.
- Langer, A.M., Nolan, R.P., 1989. Mineralogical characterization of Vanderbilt Talc Specimens. Contract analysis and report to the RT Vanderbilt Company, Inc.
- Langer, A.M., Nolan, R.P., Addison, J., 1991. Distinguishing between amphibole asbestos fibers and elongate cleavage fragments of their non-asbestos analogues. In: Brown, R.C., Hoskins, J.A., Johnson, N.F. (Eds.), *Mechanisms in Fibre Carcinogenesis*. Plenum Press, NY in Cooperation with NATO Scientific Affairs Division, pp. 253–267.
- Langer, A.M., Mackler, A.D., Pooley, F.D., 1974. Electron microscopical investigation of asbestos fibers. *Environ. Health Perspect.* 9, 63–80.
- Lanphear, B.P., Buncher, C.R., 1992. Latent period for malignant mesothelioma of occupational origin. *J. Occup. Med.* 34, 718–721.
- Lawler, A.B., Mandel, J.S., Schuman, L.M., Lubin, J.H., 1985. A retrospective cohort mortality study of iron ore (hematite) miners in Minnesota. *J. Occup. Med.* 27, 507–517.
- Lee, R.J., 1990. Letter to National Stone Association on results of width distributions of Addison and Davis tremolite samples, April 16, 1990.
- Levin, J.L., McLarty, J.W., Hurst, G.A., Smith, A.N., Frank, A.L., 1998. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. *Occup. Environ. Med.* 55, 155–160.
- Levy, R.S., Sigurdson, E., Mandel, J., Laudon, E., Pearson, J., 1976. Investigating possible effects of asbestos in city water: surveillance of gastrointestinal cancer incidence in Duluth, Minnesota. *Am. J. Epidemiol.* 103, 362–368.
- Liddell, F.D.K., McDonald, A.D., McDonald, J.C., 1997. The 1891–1920 birth cohort of Québec chrysotile miners and millers: development from 1904 and mortality to 1992. *Ann. Occup. Hyg.* 41, 13–36.
- Masson, T.J., McKay, F.W., Miller, R.W., 1974. Asbestos-like fibers in the Duluth water supply: relation to mortality. *JAMA* 228, 1019–1020.
- McConnell, E., Rutter, H.A., Ulland, B.M., Moore, J.A., 1983. Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. *Environ. Health Perspect.* 53, 27–44.
- McDonald, J.C., Harris, J., Armstrong, B., 2004. Mortality in a cohort of vermiculite miners exposed to fibrous amphiboles in Libby, Montana. *Occup. Environ. Med.* 61, 363–366.
- McDonald, J.C., Harris, J., Armstrong, B., 2002. Cohort mortality study of Vermiculite miners exposed to fibrous tremolite: an update. *Ann. Occup. Hyg.* 46 (1), 93–94.
- McDonald, J.C., McDonald, A.D., Sebastien, P., Moy, K., 1988. Health of vermiculite miners exposed to trace amounts of fibrous tremolite. *Br. J. Ind. Med.* 45, 630–634.
- McDonald, J.C., McDonald, A.D., Armstrong, B., Sebastien, P., 1986a. Cohort study of mortality of vermiculite miners exposed to tremolite. *Br. J. Ind. Med.* 43, 434–444.
- McDonald, J.C., Sebastien, P., Armstrong, B., 1986b. Radiological survey of past and present vermiculite miners exposed to tremolite. *Br. J. Ind. Med.* 43, 445–449.
- McDonald, G.C., Gibbs, G.W., Liddell, F.D.K., McDonald, A.D., 1978. Mortality after long exposure to cummingtonite-grunerite. *Am. Rev. Resp. Dis.* 118, 271–277.
- Meurman, L.O., Pukkala, E., Hakama, M., 1994. Incidence of cancer among anthophyllite asbestos miners in Finland. *Occup. Environ. Med.* 51, 421–425.
- Meurman, L.O., Kiviluoto, R., Kakama, M., 1974. Mortality and morbidity among the working population of anthophyllite asbestos mines in Finland. *Br. J. Ind. Med.* 31, 105–112.
- Meurman, L.O., Kiviluoto, R., Hakama, M., 1979. Combined effect of asbestos exposure and tobacco smoking on Finnish anthophyllite miners and millers. *Ann. N. Y. Acad. Sci.* 330, 491–495.
- Nolan, R.P., Langer, A.M., Oechsle, G.W., Addison, J., 1991. Association of tremolite habit with biological potential: preliminary report in mechanisms. In: Brown, R.C., Hoskins, J.A., Johnson, N.F. (Eds.), *Fibre Carcinogenesis*. Plenum Press, NY in Cooperation with NATO Scientific Affairs Division, pp. 231–251.
- Nolan, R.P., Langer, A.M., Wilson, R., 1999. A risk assessment for exposure to grunerite asbestos (amosite) in an iron ore mine. *Proc. Natl. Acad. Sci. USA* 96, 3412–3419.
- Oehlert, G.W., 1991. A reanalysis of the Stanton et al. pleural sarcoma data. *Environ. Res.* 54, 194–205.
- Oestenstad, K., Honda, Y., Delzell, E., Brill, I., 2002. Assessment of historical exposures to talc at a mining and milling facility. *Ann. Occup. Hyg.* 46, 587–596.
- Pelnar, P.V., 1988. Further evidence of nonasbestos-related mesothelioma: a review of the literature. *Scand. J. Work Environ. Health* 14, 141–144.
- Pictorial Atlas of Mineral Fibers, in press. The importance of using mineral growth habits to distinguish between the potency of asbestiform and non-asbestiform fibers in the etiology of asbestos-related cancer. *Regul. Toxicol. Pharm.*

- Price, B., Ware, A., 2004. Mesothelioma trends in the United States: an update based on SEER data for 1973 through 2003. *Am. J. Epidemiol.* 159, 107–112.
- Pylev, L.N., Iankova, G.D., 1975. Carcinogenic activity of magnesite arfvedsonite (group of amphibole asbestos minerals) administered intrapleurally to nonbred rats. *Vopr. Onkol.* 21 (1), 71–76. In Russian.
- Rodelsperger, K., Bruckel, B., 2006. The carcinogenicity of WHO fibers of silicon carbide: SiC whiskers compared to cleavage fragments of granular SiC. *Inhal. Toxicol.* 18, 623–631.
- Roggli, V.L., 1990. Human disease consequences of fiber exposures: a review of human lung pathology and fiber burden data. *Environ. Health. Perspective* 88, 295–303.
- Ross, M., 1978. The 'asbestos' minerals: definitions, description, modes of formation, physical and chemical properties, and health risk to the mining community. National Bureau of Standards Special Publication 506. Proceedings of the Workshop on Asbestos: Definitions and Measurement Methods held at NBS, Gaithersburg, MD, July 18–20, 1977, pp. 49–63.
- Rubino, G.F., Scansetti, G., Piolatto, G., Romano, C.A., 1976. Mortality study of talc miners and millers. *J. Occup. Med.* 18, 187–193.
- Rubino, G.F., Scansetti, G., Piolatto, G., Gay, G., 1979. Mortality and morbidity among talc miners and millers in Italy. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Park Forest South, Illinois, pp. 357–363.
- Schiller, J.E., Payne, S.L., Khalafalla, S.E., 1980. Surface charge heterogeneity in amphibole cleavage fragments and asbestos fibers. *Science* 209, 1530–1532.
- Seidman, H., Selikoff, I.J., Hammond, E.C., 1979. Short-term asbestos work and long-term observation. *Ann. N. Y. Acad. Sci.* 330, 61–89.
- Seidman, H., Selikoff, I.J., Gelb, S.K., 1986. Mortality experience of amosite asbestos factory workers: dose–response relationships 5 to 40 years after onset of short-term work exposure. *Am. J. Ind. Med.* 10, 479–514.
- Selevan, S.G., Dement, J.M., Wagoner, J.K., Froines, J.R., 1979. Mortality patterns among miners and millers of non-asbestiform talc: preliminary Report. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Park Forest South, IL, pp. 379–388.
- Siegrist, H.G., Wylie, A.G., 1980. Characterizing and discriminating the shape of asbestos particles. *Environ. Res.* 23, 348–361.
- Sigurdson, E.E., Levy, B.S., Mandel, J., McHugh, R., Michienzi, L.J., Jagger, H., Pearson, J., 1981. Cancer morbidity investigations: lessons from the Duluth study of possible effects of asbestos in drinking water. *Environ. Res.* 25, 50–61.
- Skinner, H.C., Ross, M., Fondel, 1988. Asbestos and other fibrous materials. Oxford University Press, Oxford, pp. 1–204.
- Sluis-Cremer, G.K., Liddell, F.D.K., Logan, W.P.D., Bezuidenhout, B.N., 1992. The mortality of amphibole miners in South Africa 1946–1980. *Br. J. Ind. Med.* 49, 566–575.
- Smith, W.E., Hubert, D.D., Sobel, H.J., Marquet, E., 1979. Biologic tests of tremolite in hamsters. In: Lemen, R., Dement, J.M. (Eds.), *Dusts and Disease*. Pathotox Publisher, Park Forest South, IL, pp. 335–339.
- Stanton, M.F., 1973. Some etiological considerations in fibre carcinogenesis. In: *Biological Effects of Asbestos*. In: Bogovski, P., Gilson, J.C., Timbrell, V., Wagner, J.C. (Eds.), IARC Sci. Publication No. 8, IARC, Lyon, France, pp. 289–294.
- Stanton, M.F., Layard, M., Tegeris, A., Miller, E., May, M., Morgan, E., Smith, A., 1981. Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J. Natl. Cancer Inst.* 67, 965–976.
- Steenland, K., Brown, D., 1995. Mortality study of gold miners exposed to silica and nonasbestiform amphibole minerals: an update with 14 more years of follow-up. *Am. J. Ind. Med.* 27, 217–229.
- Stille, W.T., Tabershaw, I.R., 1982. The mortality experience of upstate New York talc workers. *J. Occup. Med.* 24, 480–484.
- Thompson, C.S., 1984. Consequences of using improper definitions for regulated mineral. In: *Definitions for Asbestos and Other Health-Related Silicates (STP-834)*. ASTM, Philadelphia, PA, p. 182.
- Timbrell, V., 1982. Deposition and retention of fibres in the human lung. *Ann. Occup. Hyg.* 26, 347–369.
- Vianna, N.J., Maslowsky, J., Roberts, S., Spellman, G., Patton, R.B., 1981. Malignant mesothelioma; epidemiologic patterns in New York State. *N. Y. State J. Med.* 81, 735–738.
- Virta, R.L., 1985. The phase relationship of talc and amphiboles in a fibrous talc sample, U.S. Department of the Interior, Bureau of Mines Report of Investigations No. 8923.
- Virta, R.L., Shedd, K.B., Wylie, A.G., Snyder, J.G., 1983. Size and shape characteristics of amphibole asbestos (amosite) and amphibole cleavage fragments (actinolite, cummingtonite) collected on occupational air monitoring filters, Chapter 47. In: Marple, V.A., Liu, B.Y.H. (Eds.), *Aerosols in the Mining and Industrial Work Environments*, Volume 2 Characterisation, Ann Arbor Science Publishers, Ann Arbor, Michigan, pp. 633–643.
- Wagner, J.C., Chamberlain, M., Brown, R.C., Berry, G., Pooley, F.D., Davies, R., Griffiths, D.M., 1982. Biological effects of tremolite. *Br. J. Cancer* 45, 352–360.
- Wagner, J.C., Berry, G., 1969. Mesotheliomas in rats following inoculation with asbestos. *Br. J. Cancer* 23, 567–581.
- Wergeland, E., Andersen, A., Baerheim, A., 1990. Morbidity and mortality in talc-exposed workers. *Am. J. Ind. Med.* 17, 505–513.
- Wild, P., Leodolter, K., Refregier, M., Schnidt, H., Zidek, T., Haidinger, G., 2002. A cohort mortality study and nested case-control study of French and Austrian talc workers. *Occup. Environ. Med.* 59, 98–105.
- Wilson, R., McConnell, E.E., Ross, M., Axten, C.W., Nolan, R.P., 2008. Risk assessment due to environmental exposures to fibrous particulates associated with taconite ore. *Regul. Toxicol. Pharm.* 52, S232–S245.
- Wylie, A.G., Virta, R.L., Segretti, J.M., 1987. Characterization of mineral population by index particle: implication for the Stanton Hypothesis. *Environ. Res.* 43, 427–439.
- Wylie, A.G., Skinner, H., Marsh, J., Snyder, H., Garzzone, C., Hodgkinson, D., Winters, R., Mossman, B., 1997. Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. *Toxicol. Appl. Pharmacol.* 147, 143–150.
- Wylie, A.G., 1988. Relationship between the growth habit of asbestos and the dimensions of asbestos fibers. *Mining Eng.* 40, 1036–1040.
- Wylie, A.G., Bailey, K.F., Kelse, J.W., Lee, R.J., 1993. The importance of width in asbestos fiber carcinogenicity and its implications for public policy. *Am. Ind. Hyg. Assoc. J.* 54, 239–252.